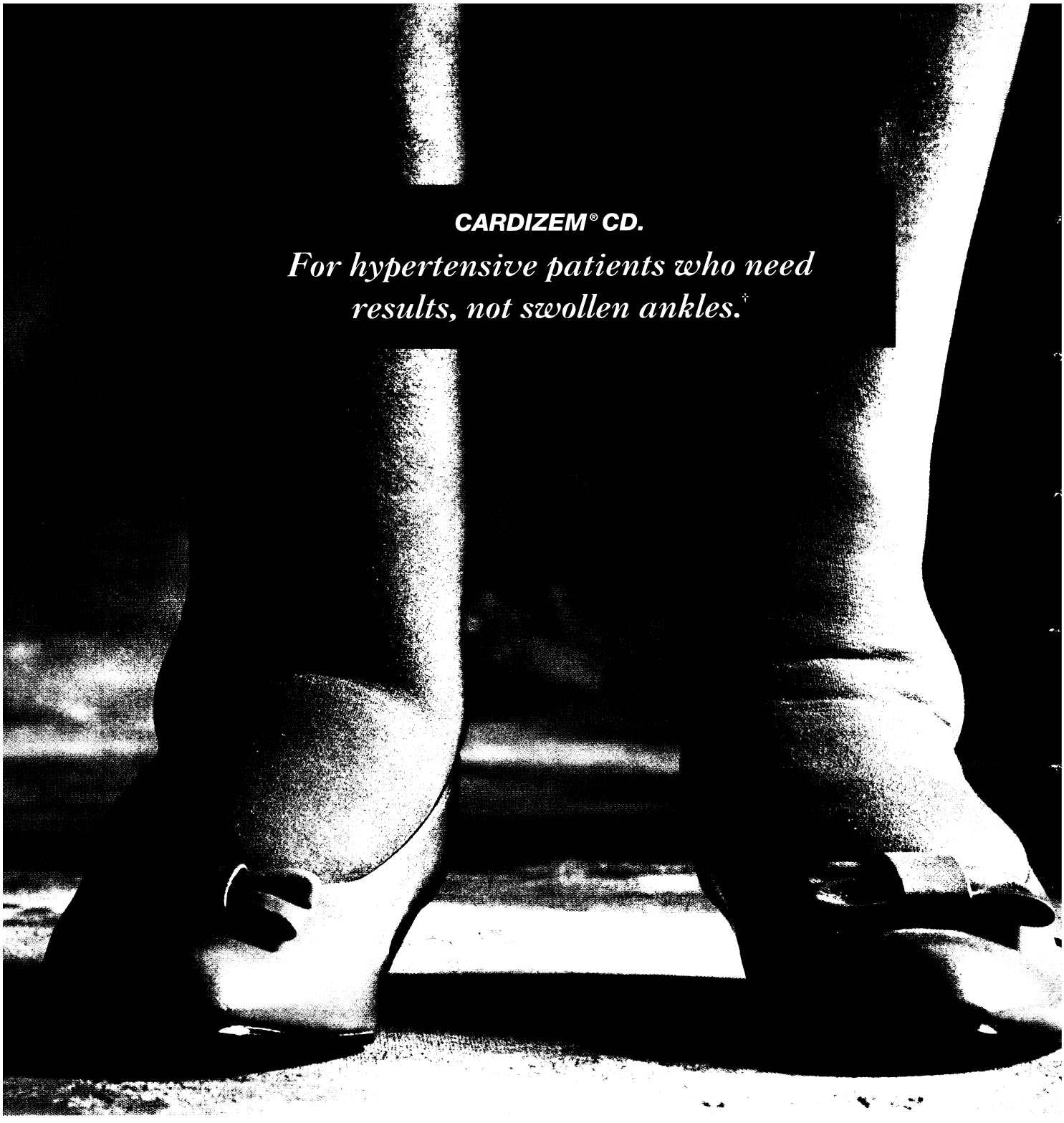


**CARDIZEM® CD.**

*For hypertensive patients who need results, not swollen ankles.†*

*Your patients don't feel their hypertension. They shouldn't feel their medication.*

Once-a-day

**CARDIZEM® CD**

Controlled Delivery diltiazem HCl/NORDIC

NORDIC LABORATORIES

Subsidiary of Marion Merrell Dow Canada

† Incidence of edema: 2.6%. For the full list of side effects (including first degree AV block), please see the BPI provided in this journal or the product monograph.

® Cardizem is a registered trademark of Marion Merrell Dow Inc., U.S.A.

MEMBER PMAC PAAB

PROCACD 94001A-E

Myocardial function declines as part of the normal aging process.[1] Some calcium channel blockers may produce a small yet significant decrease in cardiac contractility, which may be unwanted.[1] On the other hand, because **RENEDIL** is so highly vasoselective, it has **NO** significant effect on cardiac conduction and contractility.[1,2] **RENEDIL** can also provide smooth 24-hour hypertension control with no clinically significant effect on heart rate.[3,†]

**And RENEDIL therapy can save more than $300 per year over other calcium antagonists.[4]**

**2.5 mg / 5 mg / 10 mg**
Extended Release Tablets

**HIGHLY VASOSELECTIVE/ONCE-A-DAY**

# RENEDIL®

felodipine

**EXCELLENT CARDIAC SAFETY PROFILE**

†Heart rate increases of 5-10 beats per minute may be seen during chronic administration.[2]

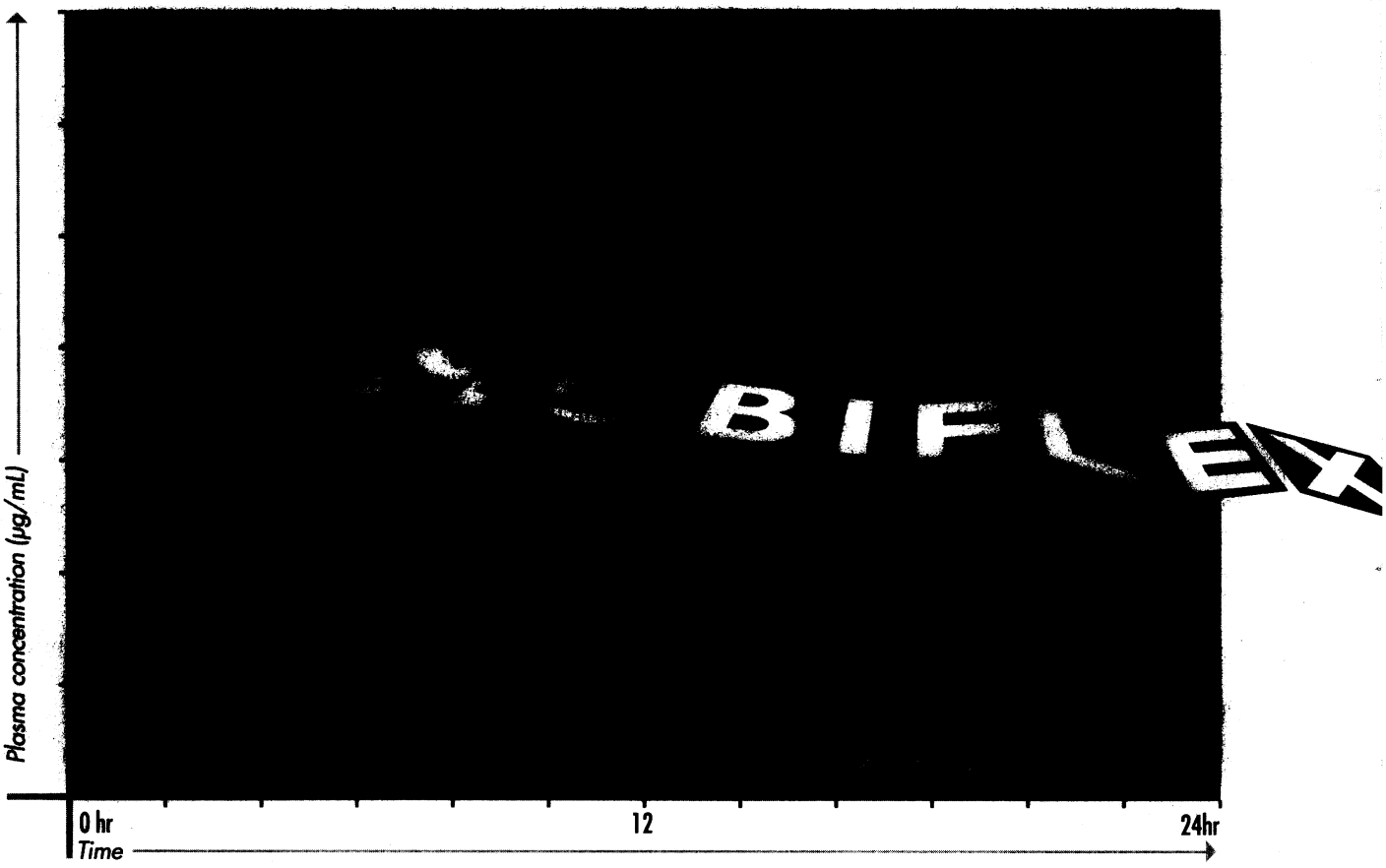
*Normally used in patients in whom diuretics or beta-blockers were found ineffective, or associated with unacceptable adverse effects.*

**Hoechst-Roussel Canada Inc.**
Montréal, Québec

PAAB ADREN 03/94

®Reg. Trademark of Hoechst AG, Germany

# 24 hour arthritis relief starts with dependable serum levels.




*24 hour inherent control instead of sustained release drug delivery* helps minimize absorption-related serum peaks and troughs that can be caused by normal variations in GI transit time and pH.[1-4]

Dependable serum levels/dependable symptom control:

- helps reduce breakthrough pain[5]
- helps reduce morning stiffness[6]
- promotes a full night's rest[6,7]

According to a review of double-blind studies, 'Mobiflex' is at least as well, or better tolerated than diclofenac, naproxen, indomethacin, and ketoprofen[8-10†]

†As with all NSAIDs, caution should be used with the elderly: the most common adverse events are g.i. related

Hoffmann-La Roche Limited, Mississauga, Ontario L5N 6L7 ®Registered Trademark

PAAB

ONCE-A-DAY

**MOBIFLEX®** 24 hr CONTROL

20 mg

TENOXICAM

Inherent control of arthritis pain and inflammation

# Once-a-day Nizoral* cream. Highly effective relief for patients overwhelmed by tinea pedis.

If your patients find "athlete's foot" hard to deal with, they're not alone: tinea pedis has become the most common fungal infection today.[1]

Your patients can rely on the efficacy of Nizoral cream. Its rapid penetration and long-lasting activity at the site of infection[2] produce clinical response rates of up to 92%.[3] These are just the results you would expect from the original once-a-day topical antifungal.[4]

There is no systemic absorption of Nizoral cream detectable in man. And it is generally well tolerated, with a 5% incidence of side effects consisting mainly of local irritation.[4]

With this combination of benefits, it's easy to see how Nizoral cream has become the topical antifungal physicians prescribe most for tinea pedis.[5,6]

**Nizoral**

**ketoconazole cream 2%**

**The #1 topical antifungal prescribed for dermatophyte conditions.[5,6]**

BEFORE PRESCRIBING, PLEASE CONSULT ENCLOSED PRESCRIBING INFORMATION

**NOT RECOMMENDED DURING PREGNANCY**

MERCK FROSST

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DIV. OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC



RNT-94-CDN-7457-JA

PAAB

**For Many of Your Hypertensive Patients, Including those with ...**

- Diabetes
- Hyperlipidemia
- Heart Failure
- Side Effects with other medications

# OFFERS MORE THAN BLOOD PRESSURE CONTROL

FOR MANY PATIENTS

Pr **VASOTEC®**

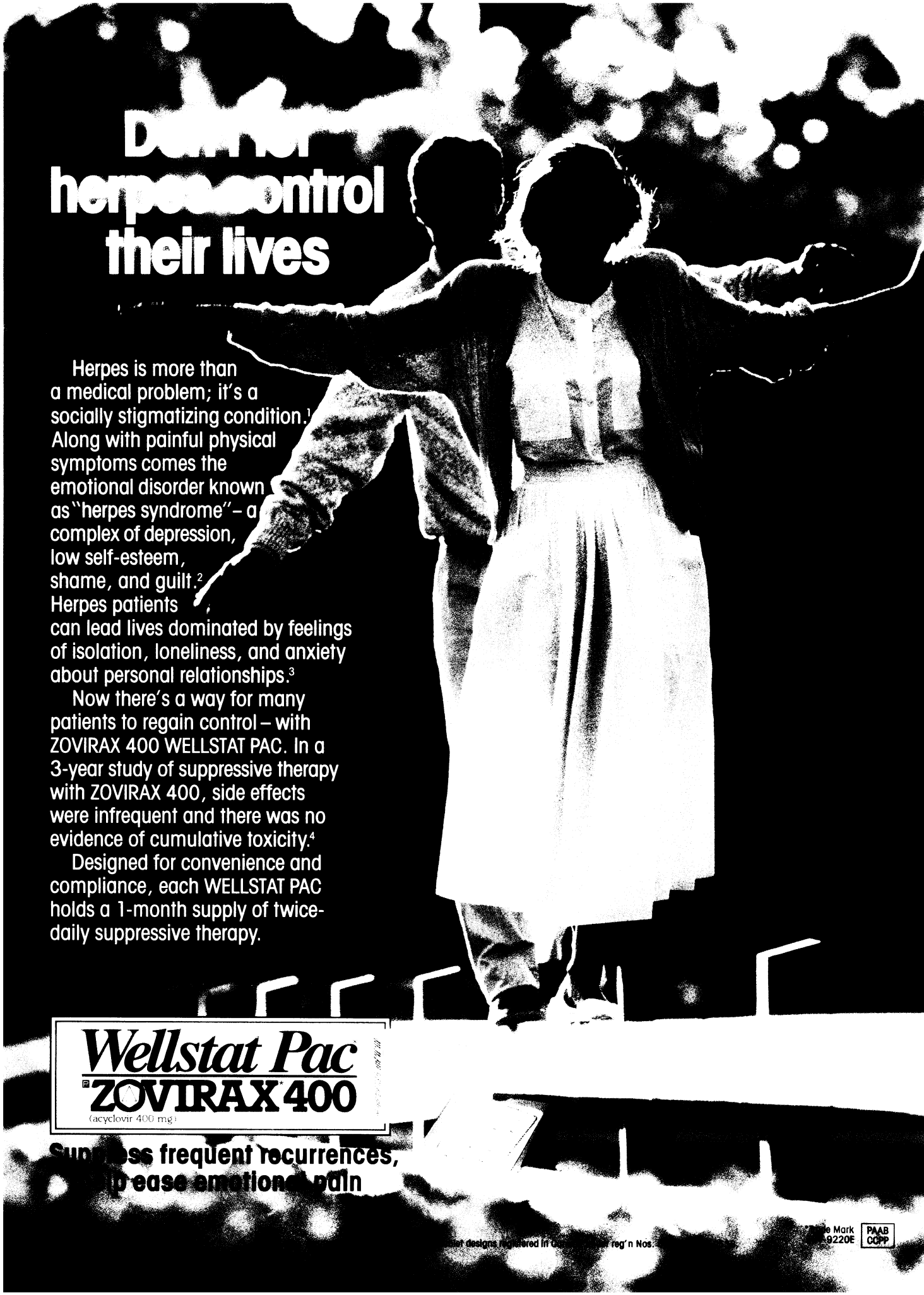
(enalapril maleate tablets, Frosst Std.)

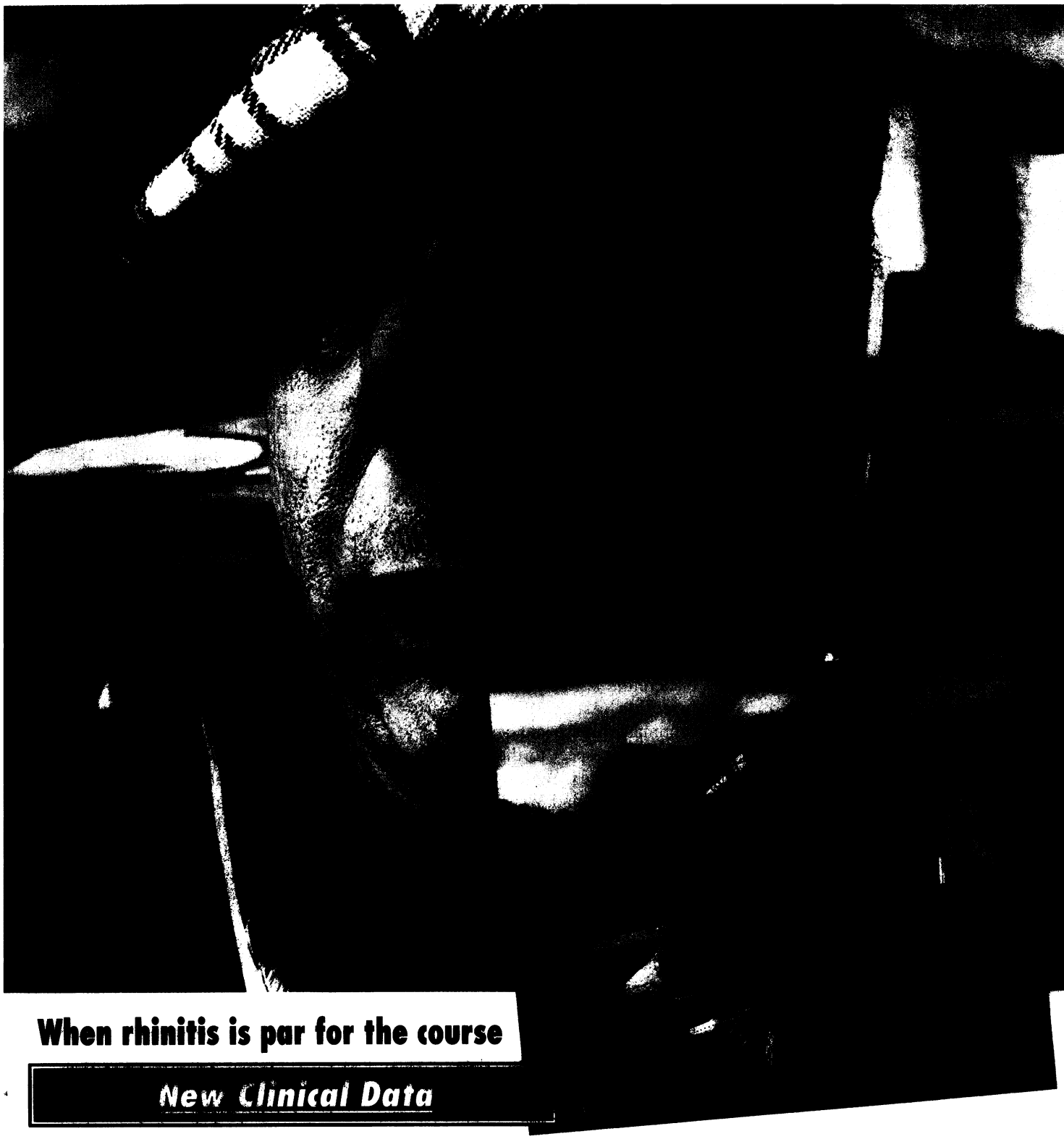
ANGIOTENSIN CONVERTING ENZYME INHIBITOR

## Daily...ONCE!!

Indicated in essential hypertension when diuretics or beta-blockers are inappropriate

For prescribing information see page 1344


Herpes is more than a medical problem; it's a socially stigmatizing condition.[1] Along with painful physical symptoms comes the emotional disorder known as "herpes syndrome" – a complex of depression, low self-esteem, shame, and guilt.[2] Herpes patients can lead lives dominated by feelings of isolation, loneliness, and anxiety about personal relationships.[3]
Now there's a way for many patients to regain control – with ZOVIRAX 400 WELLSTAT PAC. In a 3-year study of suppressive therapy with ZOVIRAX 400, side effects were infrequent and there was no evidence of cumulative toxicity.[4]
Designed for convenience and compliance, each WELLSTAT PAC holds a 1-month supply of twice-daily suppressive therapy.
Wellstat Pac
ZOVIRAX 400
(acyclovir 400 mg)



# When rhinitis is par for the course

## New Clinical Data

A recent Canadian clinical trial concluded that in 41% of patients with allergic rhinitis, once daily Nasacort provided *symptom relief◊ of nasal congestion within 24 hours of the first dose.*[1]

℞ once daily

**Nasacort*** Nasal Inhaler

(triamcinolone acetonide)

RHÔNE-POULENC RORER

RHÔNE-POULENC RORER CANADA INC.*
MONTRÉAL
*registered user

***Prompt* relief of allergic rhinitis symptoms◊†**

Incidence of most common side effects, headache and nasal irritation, comparable to placebo.[2]

◊25% decrease in nasal congestion from baseline (n=85, $p<0.05$). Symptom relief improvement included reduction in nasal congestion, itching of the nose/palate and combined measure of nasal symptoms. Full effect may not be achieved for 2-3 days and as long as two weeks in some patients.

†unresponsive to conventional treatment

94.486.14

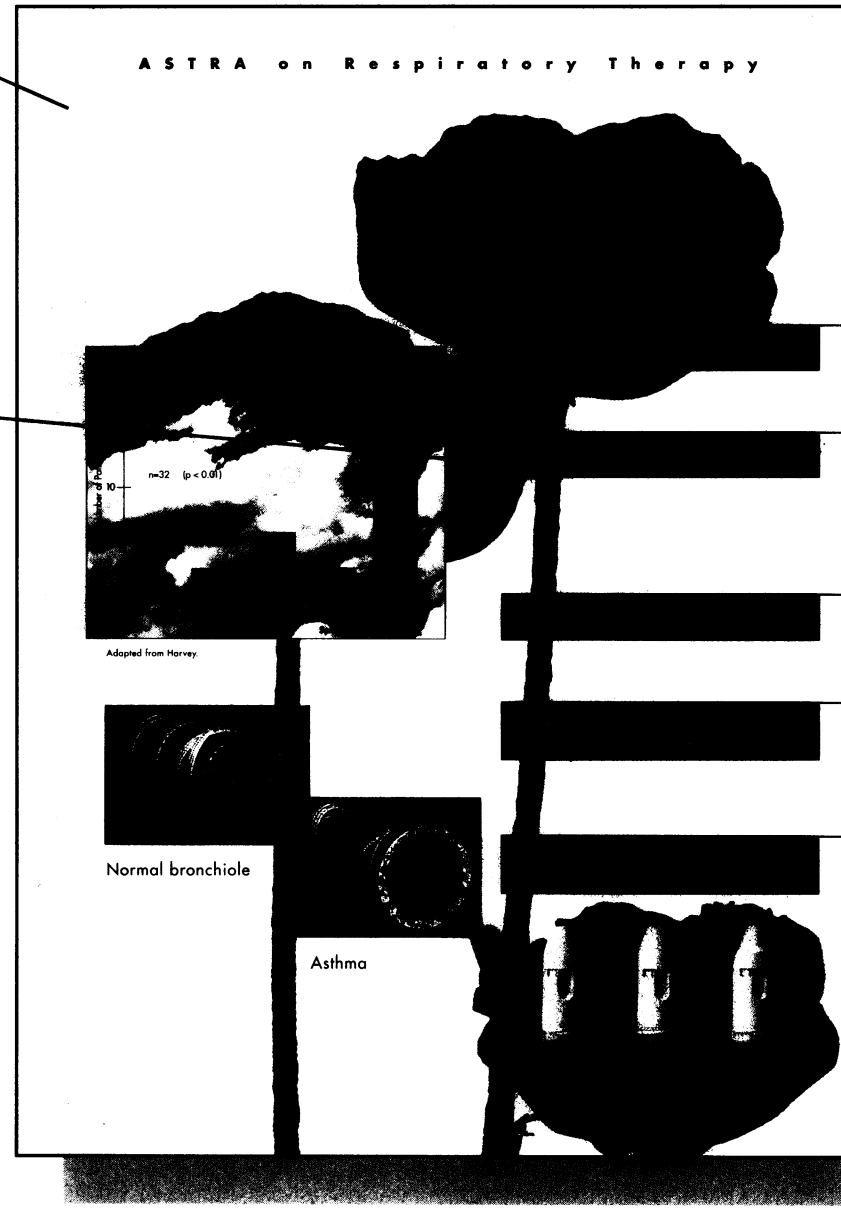
MEMBER PMAC PAAB

ASTRA
INTRODUCES A
NEW WAY TO BRING
YOU PRODUCT
INFORMATION.

# INTRODUCING THE

**Each issue is colour-coded by therapeutic category for quick identification.**

**Key product information will be shown in this panel.**




Providing Canadian healthcare professionals with clear, balanced, and useful information about our products has always been Astra's goal.

But today, when it's so important to know more about pharmaceutical products, at a time when there are more products to know about, we looked for ways to better meet your needs.

So we invented a new approach. This new format is designed to give you as complete a story as possible – at a glance. Clearly. Succinctly. Factually.

It was designed in co-operation with Canadian healthcare professionals after indepth research showed that

# ASTRA INFO · MAT

to tell you about our products.

Turbuhaler®

# Turbuhaler®

**Pulmicort® Bricanyl® Rhinocort®**

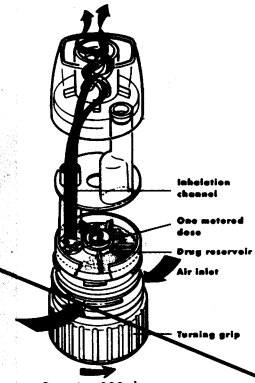
(Budesonide 100 µg, 200 µg, 400 µg) (Terbutaline sulfate 500 µg) (Budesonide 100 µg)

Turbuhaler® is a unique delivery system available with Bricanyl® and Pulmicort® for the treatment of asthma; and with Rhinocort® for the treatment of perennial and seasonal rhinitis.

Turbuhaler® is the first pre-loaded, breath-activated, dry powder delivery system. It delivers only active drug (no propellants or additives). Turbuhaler® is an easy to use delivery system that studies show patients prefer.[1-4]

Patients can use the same highly effective delivery system for both asthma and rhinitis treatments.[2,5]

Patients should be reminded that due to the small amount of drug delivered they may not taste or feel any medication when inhaling from Turbuhaler.®[6,7,8]



Contains 200 doses

For further information on Turbuhaler® call the Astra Customer Relations Team at 1-800-668-6000 or 905-275-4015 for local calls in the Toronto area.


1. Harvey J, et al. Randomised cross-over comparison of five inhaler systems for bronchodilator therapy. Br J Clin Pract 1992; 46: No 4.
2. Engel T, et al. Clinical comparison of inhaled budesonide delivered either via pressurized metered dose inhaler or Turbuhaler.® Allergy 1989; 44: 220-225.
3. Aalto E, et al, Comparison of terbutaline Turbuhaler and albuterol chlorofluorocarbon (CFC) inhaler in middle-aged and elderly patients with obstructive lung disease. Ann Allergy 1992; 69: 33-36.
4. Hultquist C, et al. A double-blind comparison between a new multi-dose powder inhaler (Turbuhaler®) and metered dose inhaler in children with asthma. Allergy 1989; 44: 467-470.
5. Pedersen B, et al. Powder administration of pure budesonide for the treatment of seasonal allergic rhinitis. Allergy 1991; 46: 582-587.
6. Pulmicort® Turbuhaler® Product Monograph.
7. Bricanyl® Turbuhaler® Product Monograph.
8. Rhinocort® Turbuhaler® Product Monograph.
9. Data on file. Communication Trends in Healthcare. SMW Research Ltd. 1993.


ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

TAB OFF PENNE

**This bar identifies the product's indication or clinical use.**

**Here's where you'll find the benefits to you and information for your patients.**

"Tell me, don't sell me" was the way in which they most appreciated receiving product information.[9]

Astra is proud to be a leader in making the goal of a true partnership between healthcare professionals and pharmaceutical manufacturers a working reality.

ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

**NEW**
**ISOPTIN SR 180 mg**
**Available on British Columbia, Saskatchewan, Manitoba and Quebec formularies**

# Going easy on your elderly hypertensives†

- Proven DBP (diastolic blood pressure) reduction in patients ≥ 60 years[1] (↓11.52 mm HG, n= 990). †Lower dosages of Isoptin SR i.e. 120 mg a day may be warranted in elderly patients
- Proven effective in elderly hypertensive patients who were newly diagnosed or had hypertension for over 20 years (↓10.6 mm HG )[1]
- Very well tolerated[1]

**Most frequently reported side effects with lower dosages of ISOPTIN SR in a study that included 990 elderly hypertensives treated with 180 mg†††**

| SIDE EFFECT | INCIDENCE* (%) |
|---|---|
| Constipation | 2.5 |
| Headache | 1.5 |
| Dizziness | 1.1 |

††AV block was not reported in any of the 990 elderly patients. n=3,851

- Priced responsibly: $31.63 per month**

***Excellent BP††† control and very few side effects at reasonable cost for your elderly hypertensives[1]***

ONCE-A-DAY

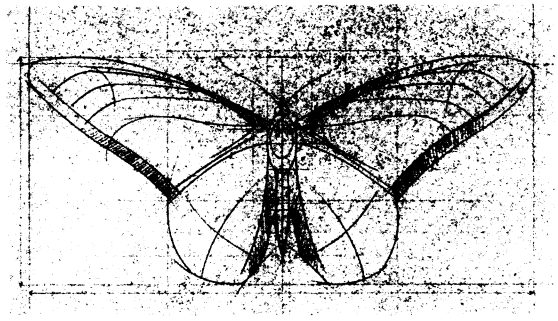
Isoptin® SR 180

(verapamil HCl sustained release tablets)
ONE DRUG. ONCE A DAY.

††† Should normally be used when diuretics or beta-blockers are unacceptable.
* Side effects may be more frequent in the elderly at higher doses.
** Not including dispensing fees that vary by province.

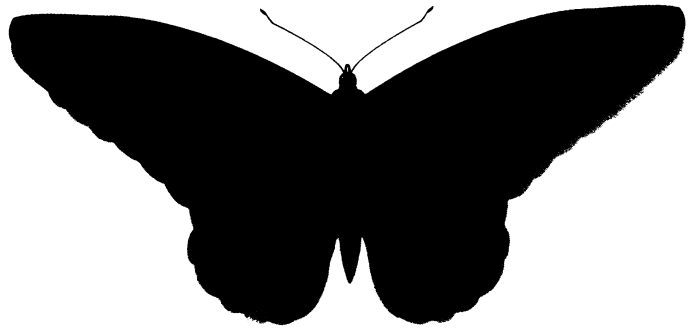
SEARLE PAAB

# *A blueprint for effective cholesterol management*



*As an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia, when diet and other nonpharmacologic measures alone have been inadequate*

## ZOCOR®
## *Designed for efficacy*



## *Consider the efficacy of ZOCOR®*

In one clinical study, (50 patients on ZOCOR®) at the starting dose of ZOCOR® 10 mg once-a-day:

- patients achieved a mean reduction in LDL-cholesterol of 33% [1]
- 70% of patients achieved ≥ 20% reduction of total cholesterol [1]

## *Significant clinical experience* [2]

- long-term experience exceeding 5 years
- over 1 200 000 patients treated worldwide
- clinical studies with 21 000 patients

**Pr ZOCOR®**

(simvastatin)

*Effective therapy against hypercholesterolemia*†

**BEFORE PRESCRIBING, PLEASE CONSULT PRESCRIBING INFORMATION.**

† The effects of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality have not been established. Generally well-tolerated - in controlled clinical trials, 1.0% of patients were withdrawn due to adverse experiences attributable to ZOCOR®.

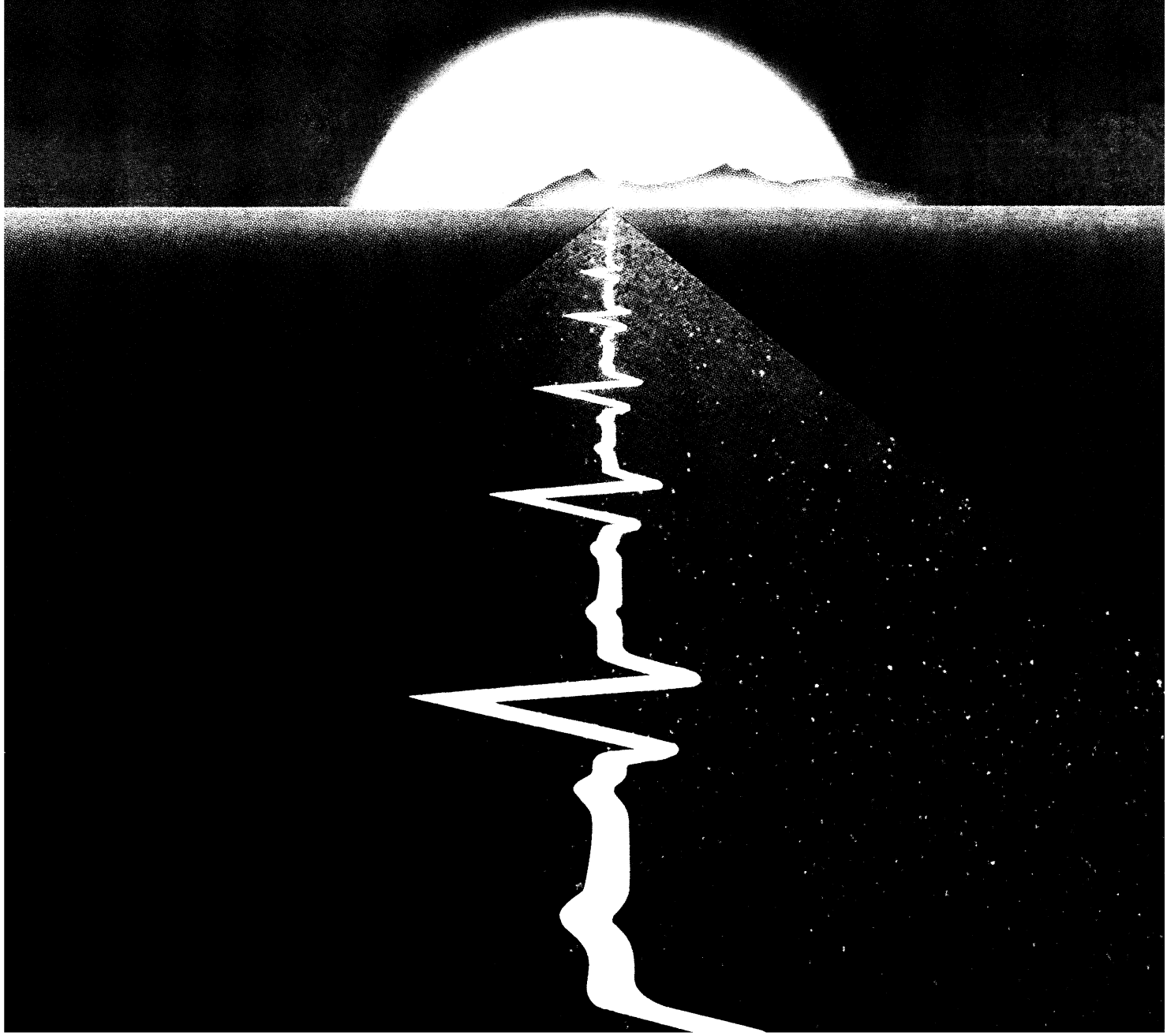
MERCK FROSST

PAAB

®Trademark Merck & Co., Inc./Merck Frosst Canada Inc., R.U. ZCR-93-CDN-6549-JA

**FROSST**
DIV. OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC

# Every so often something comes along that can change the way you manage your angina patients



*INTRODUCING*

# Highly Predictable Angina Control...

# Now. Throughout the Day. Every Day.

- **Control that provides significant fast-acting prophylaxis within 1 hour[1]**
- **Control that lasts for up to 12 hours[2]**
- **Control that helps avoid tolerance[1,3] through a unique dosage schedule**
- **Control that offers one consistent dosage for all patients[4]**

*Registered user. Sold under licence from Boehringer Mannheim Canada Ltd.

Headaches or symptoms of hypotension, such as weakness or dizziness, may occur. Thus, reaction time when driving or operating machinery may be impaired.

Ismo is indicated for the prevention of chronic stable angina pectoris. Not recommended for use in aborting acute anginal episodes or in patients with acute myocardial infarction or congestive heart failure.

*Please see Prescribing Information on the next page.*

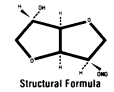
# Ismo

*(isosorbide-5-mononitrate)*

**20 mg twice daily, dosed 7 hours apart**

## Highly Predictable Angina Control... Now. Throughout the Day. Every Day.

**THERAPEUTIC CLASSIFICATION** Antianginal Agent. **ACTION AND CLINICAL PHARMACOLOGY** As with other organic nitrates, the principal pharmacological action of ISMO (isosorbide-5-mononitrate), the major active metabolite of isosorbide dinitrate (ISDN), is relaxation of vascular smooth muscle and consequent dilation of peripheral arteries and veins, especially the latter. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (after-load). Dilation of the coronary arteries also occurs. The hemodynamic responses to isosorbide-5-mononitrate are similar to those produced by other nitrates. **Pharmacodynamics:** Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Prolonged administration of nitrate drugs according to traditionally recommended dosage regimens has been shown to produce tolerance. Tolerance results in a loss of efficacy. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously-delivered nitrates. In the large majority of these trials, nitrate effectiveness was indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored. Drug-free intervals of 10 to 12 hours are known to be sufficient to restore response. The drug-free interval sufficient to avoid tolerance to isosorbide-5-mononitrate has not been completely defined. In the only regimen of twice-daily ISMO (isosorbide-5-mononitrate) the two doses are given 7 hours apart. This asymmetric twice-daily regimen provides antianginal efficacy for up to 12 hours (i.e. 7 hours between doses and 5 hours after second dose). Considering the pharmacokinetic profile of isosorbide-5-mononitrate and its long half-life (see **Pharmacokinetics**), clinical efficacy is consistent with that observed for other organic nitrates. **Pharmacokinetics:** In humans, isosorbide-5-mononitrate is not subject to significant first pass metabolic changes in the liver. The absolute bioavailability of isosorbide-5-mononitrate from tablets is nearly 100%. The absorption is rapid, and maximum serum concentrations are achieved 30 to 60 minutes after dosing. The volume of distribution of isosorbide-5-mononitrate is approximately 0.6 L/kg, and less than 4% is bound to plasma proteins. It is cleared from the serum by denitration to isosorbide; glucuronidation to the mononitrate glucuronide; and denitration/hydration to sorbitol. None of these metabolites is vasoactive. Less than 1% of administered isosorbide-5-mononitrate is eliminated in the urine. The overall elimination half-life of isosorbide-5-mononitrate is about 5 hours; the rate of clearance is the same in healthy young adults, in patients with various degrees of renal, hepatic, or cardiac dysfunction, and in the elderly. **INDICATIONS AND CLINICAL USE** ISMO (isosorbide-5-mononitrate) is indicated for the prevention of anginal attacks in patients with chronic stable angina pectoris associated with coronary artery disease. ISMO is not intended for the immediate relief of acute attacks of angina pectoris. **CONTRAINDICATIONS** 1. Known hypersensitivity to isosorbide mononitrate or to other nitrates or nitrites. 2. Acute circulatory failure associated with marked hypotension (shock and states of collapse). 3. Postural hypotension. 4. Myocardial insufficiency due to obstruction (e.g. in the presence of aortic or mitral stenosis or of constrictive pericarditis). 5. Increased intracranial pressure. 6. Increased intraocular pressure. 7. Severe anemia. **WARNINGS** The benefits and safety of ISMO (isosorbide-5-mononitrate) in anginal patients with acute myocardial infarction or congestive heart failure have not been established. Because the effects of isosorbide mononitrate are difficult to terminate rapidly, this drug is not recommended in these settings. **PRECAUTIONS** Headaches or symptoms of severe hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. Caution should be exercised when using nitrates in patients prone to, or who might be affected by hypotension. ISMO (isosorbide-5-mononitrate) should therefore be used with caution in patients who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g., below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. There is moreover, physical dependence since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers. In clinical trials of angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The importance of these observations to the routine, clinical use of oral isosorbide mononitrate has not been fully elucidated. Caution should be exercised in patients with arterial hypoxemia due to anemia (see **Contraindications**). Similarly, caution is called for in patients with hypoxemia and a ventilation/perfusion imbalance due to lung disease or ischemic heart failure. Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, isosorbide-5-mononitrate could reverse this protective vasoconstriction and thus result in increased perfusion to poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.Tolerance to isosorbide-5-mononitrate with cross tolerance to other nitrates or nitrites may occur (see **Action And Clinical Pharmacology**). As tolerance to isosorbide-5-mononitrate develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment. **Use in Pregnancy:** In rats receiving isosorbide-5-mononitrate 500 mg/kg/day (125 X the human exposure comparing body surface area) there were small but statistically significant increases in the rates of prolonged gestation, prolonged parturition, stillbirth, and neonatal death; and there were small but statistically significant decreases in birth weight, live litter size, and pup survival. At 250 mg/kg/day, no adverse effects on reproduction and development were reported. In rats and rabbits receiving isosorbide-5-mononitrate at up to 250 mg/kg/day, no developmental abnormalities, fetal abnormalities, or other effects on reproductive performance were detected; these doses are larger than the maximum recommended human dose by factors between 70 (body-surface-area basis in rabbits) and 310 (body-weight basis, in either species). There are no studies in pregnant women. Isosorbide-5-mononitrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Use in Nursing Mothers:** It is not known whether isosorbide-5-mononitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide-5-mononitrate is used to treat a nursing woman. **Use in Children:** The safety and effectiveness of isosorbide-5-mononitrate in children have not been established. Therefore, its use is not recommended. **Drug Interactions:** Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquilizers may potentiate the blood pressure lowering effect of ISMO. Alcohol may enhance sensitivity to the hypotensive effects of nitrates. Concurrent administration of ISMO with dihydroergotamine may increase the bioavailability of dihydroergotamine. Special attention should be paid to this point in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitrates and may lead to coronary vasoconstriction. **Information For Patients:** Patients should be told that in order to maintain the antianginal efficacy of ISMO tablets they must carefully follow the prescribed schedule of dosing (two doses taken seven hours apart) in a 24-hour period. For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours later. As with other nitrates, headache may occur during therapy with ISMO. Patients who get these headaches, should not alter the schedule of their treatment with ISMO, since loss of headache may be associated with simultaneous loss of antianginal efficacy. Headaches may be relieved by the use of standard analgesics, such as aspirin or acetaminophen. Treatment with isosorbide-5-mononitrate may be associated with light-headedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol. **ADVERSE REACTIONS** In controlled clinical trials 20 mg twice daily of ISMO (isosorbide-5-mononitrate) was administered to 219 patients alone or in combination with beta-adrenergic blocking agents. Adverse reactions were reported in 47% of patients. Discontinuation of therapy due to adverse reactions was required in 11% of patients. Most of these discontinued because of headache. Dizziness, nausea and chest pain were also frequently associated with withdrawal from these studies. The most common adverse reactions (incidence of at least 1%) were: headache, nausea, dizziness, flu-like symptoms, chest pain and rash. In addition, the following adverse reactions were reported with an incidence lower than 1% in controlled as well as other studies in which 3344 patients received 5 to 240 mg per day in a variety of regimens: *Cardiovascular:* angina pectoris, arrhythmias, atrial fibrillation, hypotension, palpitations, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope. *Dermatological:* pruritus, rash. *Gastrointestinal:* abdominal pain, diarrhoea, dyspepsia, tenesmus, vomiting. *Genitourinary:* dysuria, impotence, urinary frequency. *Miscellaneous:* asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors. *Musculoskeletal:* arthralgia. *Neurological:* agitation, anxiety, confusion, dyscoordination, hypoesthesia, hypokinesia, increased appetite, insomnia, nervousness, nightmares. *Respiratory:* bronchitis, pneumonia, upper respiratory tract infection. Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia; for further discussion of its diagnosis and treatment see **Symptoms and Treatment of Overdosage**. **SYMPTOMS AND TREATMENT OF OVERDOSAGE** HEMODYNAMIC EFFECTS: Symptoms of ISMO (isosorbide-5-mononitrate) overdose are generally the results of vasodilation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death. No specific antagonist to the vasodilator effects of isosorbide-5-mononitrate is known, and no intervention has been subject to controlled study as a therapy of isosorbide-5-mononitrate overdose. Because the hypotension associated with isosorbide-5-mononitrate overdose is the result of venodilation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide-5-mononitrate overdose in these patients may be subtle and difficult, and invasive monitoring may be required.The use of epinephrine or other arterial vasoconstrictors is ineffective in reversing the severe hypotensive effects of overdose and is therefore contraindicated in this situation. Dialysis is known to be ineffective in removing isosorbide-5-mononitrate from the body. METHEMOGLOBINEMIA: Methemoglobinemia has been reported in patients receiving other organic nitrates, and it may occur as a side effect of isosorbide-5-mononitrate. Nitrate ions liberated during metabolism of isosorbide-5-mononitrate can oxidize hemoglobin into methemoglobin. In patients totally without cytochrome $b_5$ reductase activity, about 2 mg/kg of isosorbide-5-mononitrate would be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin would require even larger doses of isosorbide-5-mononitrate. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial $pO_2$. Classically, methemoglobinemic blood is described as chocolate brown without colour change on exposure to air. When methemoglobinemia is diagnosed, administration of methylene blue, 1 to 2 mg/kg intravenously, may be required. **DOSAGE AND ADMINISTRATION** The daily dosage schedule is designed to avoid or attenuate the development of tolerance to ISMO (isosorbide-5-mononitrate). Patients should be watched carefully for an increase in angina pectoris during the drug-free period. Adjustment of background medication may be required. The recommended dose of ISMO (isosorbide-5-mononitrate) is 20 mg twice daily given 7 hours apart. For those patients who are active during the day, this can be accomplished by taking the first dose upon awakening and the second dose 7 hours later. Dosage adjustments are not necessary for elderly patients or patients with altered renal or hepatic function. The 20 mg twice daily dose should not be exceeded and doses lower than that are not recommended. Limited clinical experience has shown that the 10 mg twice daily dose was not unequivocally better than placebo, while the effect of the 40 mg twice daily dose was similar to that of the 20 mg dose. The 60 mg twice daily dose appeared to be less effective and was associated with an increased incidence of adverse reactions and a rebound phenomenon. **PHARMACEUTICAL INFORMATION** Chemically, isosorbide-5-mononitrate is 1,4:3,6-dianhydro-D-glucitol,5-nitrate. The nitrate ester in the 5-position of isosorbide-5-mononitrate exists in the endoconfiguration. This provides a degree of stearic protection from denitration, and is responsible for the long half-life of isosorbide-5-mononitrate. Because of the potentially explosive nature of pure isosorbide-5-mononitrate, it is supplied as a trituration with lactose. **Drug Substance:** *Proper Name:* Isosorbide-5-mononitrate. *Chemical Name:* 1,4:3,6-dianhydro-D-glucitol,5-nitrate. *Molecular Weight:* 191.14. *Physical Form:* Isosorbide-5-mononitrate is an odourless, white, fine, crystalline powder. *Solubility:* It is freely soluble in water, methanol, acetone, and ethanol. *Melting Point Range:* 87° to 90°C. *Composition:* Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, Hydroxypropyl Methylcellulose, Povidone, Magnesium Stearate, Silicon Dioxide, Polyethylene Glycol, Polysorbate 20, SDA-3A Ethyl Alcohol, D & C Yellow No. 10, FD & C Yellow No. 6, Titanium Dioxide, Hydroxypropyl Cellulose. *Stability and Storage Recommendations:* Store at controlled room temperature, between 15°C and 30°C. Dispense in tight containers. **AVAILABILITY OF DOSAGE FORMS** ISMO 20 mg is available in bottles of 100 tablets. Each tablets is orange, biconvex, round, film-coated and engraved with "ISMO 20" on one side and "W" on the other side.



Structural Formula

*Product Monograph available on request.*

**References: 1.** Friedman RG, ISMN Study Group. Comparative clinical trial of isosorbide mononitrate and isosorbide dinitrate in patients with stable angina pectoris. *J Invas Cardiol.* 1992;4:319-329. **2.** Thadani U, Maranda CR, Amsterdam E, et al. Lack of pharmacologic tolerance and rebound angina pectoris during twice daily therapy with isosorbide-5-mononitrate. *Ann Intern Med.* (In press.) **3.** Parker JO. ISMN Study Group. Eccentric dosing with isosorbide-5-mononitrate in angina pectoris. *Am J Cardiol.* 1993;72:871-876. **4.** Product Monograph for Ismo (isosorbide-5-mononitrate), Wyeth-Ayerst Canada Inc.

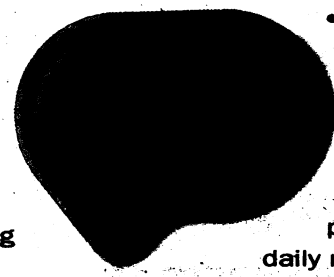
February 1994 Printed in Canada


PAAB CCPP

WYETH-AYERST CANADA INC.
Montreal, Canada H3R 1J6

Whenever Transderm-Nitro is applied, patients know their therapy is at work.

- **Transderm-Nitro** is applied once a day, and worn for 12 to 14 hours (versus the multiple dosing of oral nitrates).
- **Transderm-Nitro** is preferred over oral nitrates: convenience of once daily dosing preferred by patients by almost 8 to 1[1]



- **Transderm-Nitro** provides the dose flexibility you need: 0.2, 0.4 and 0.6 mg/hour strengths.
- **Transderm-Nitro** helps protect against tolerance[2,3] "Patch on – patch off" intermittent dosing for a daily nitrate-free interval.

*Like all nitrates, headaches or symptoms of hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. A reduction in dose or discontinuation of treatment may be necessary. TRANSDERM-NITRO is not intended for the immediate relief of acute attacks or angina pectoris.*

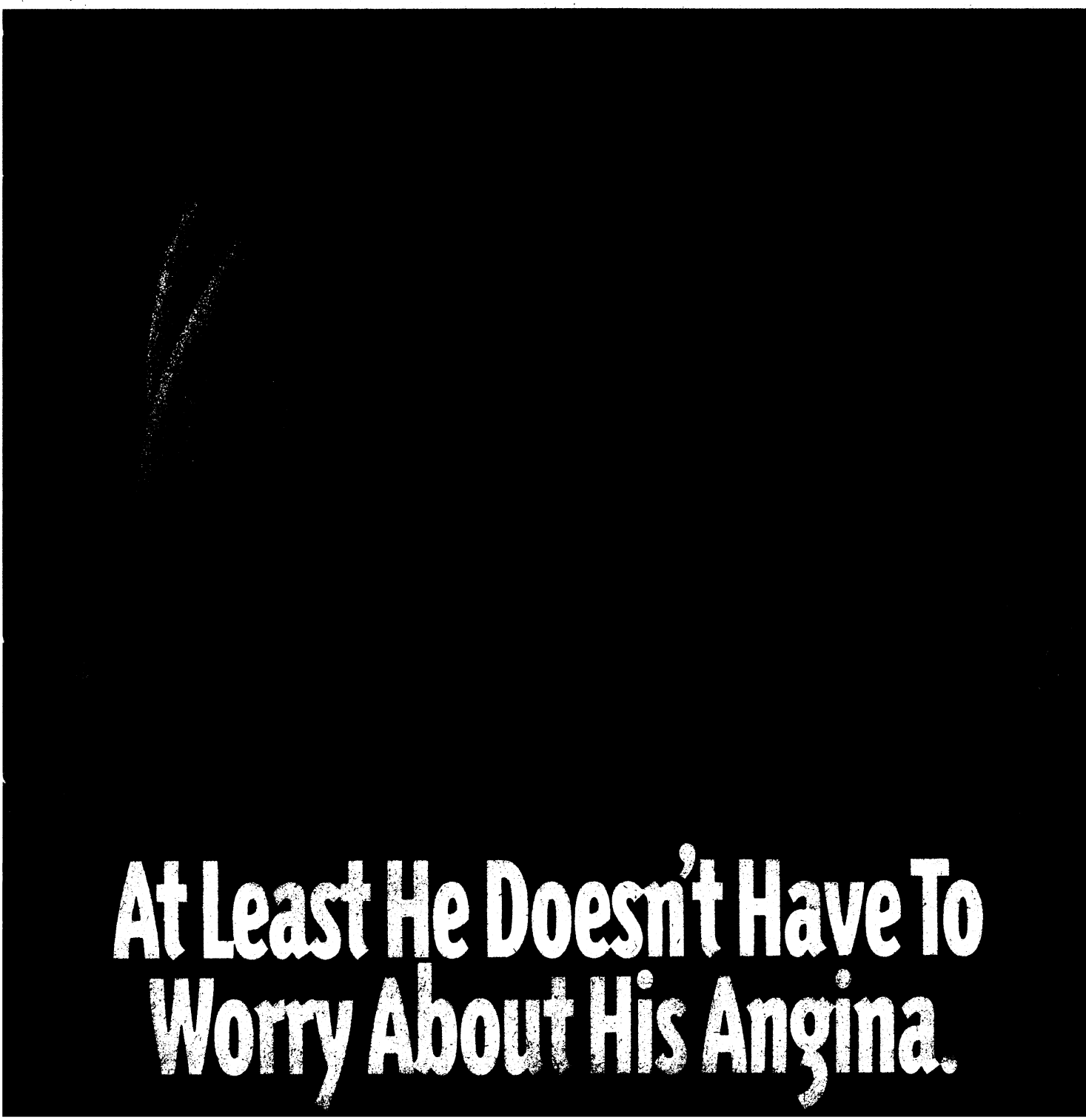
**References:** 1. Brady E, Gold O, Rosenbach H. Antianginal Efficacy of Transdermal Nitroglycerin and Oral Nitrates: The Action Study. CVR&R 1988 October: 40-44. 2. Scardi S, Camerini F, Pandullo C, Poltavini G, Collaborative Nitro Group. Efficacy of continuous and intermittent transdermal treatment with nitroglycerin in effort angina pectoris: a multicentric study. Int J Cardiol 1991; 32: 241-248. 3. Abrams J. Management of myocardial ischemia: Role of intermittent nitrate therapy. Am Heart J 1990; 120: 762-765.

ONCE • A • DAY ANTIANGINAL

**TRANSDERM-NITRO®**

(nitroglycerin)

**Offers protection when they need it most.**

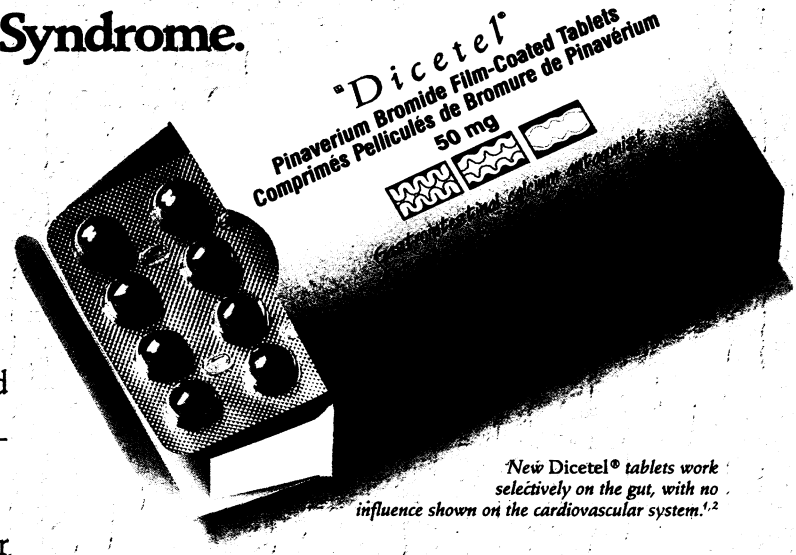


# At Least He Doesn't Have To Worry About His Angina.

Calcium antagonists help relieve spasm in vessels of the heart.

Now imagine what one could do for spasm in the gut.

# Introducing new Dicetel® tablets. The first GI calcium antagonist for the pain of Irritable Bowel Syndrome.




*New* Dicetel® *tablets work selectively on the gut, with no influence shown on the cardiovascular system.*[1,2]

The abdominal pain of Irritable Bowel Syndrome (IBS) may be the pain of unrelieved spasm. It is this pain that makes IBS so upsetting and disabling for so many patients.

But new Dicetel® tablets can offer relief.[1,3-5]

Dicetel® is the first *gastro-intestinal* calcium antagonist. It works selectively on the gut to ease muscular contraction[1] and its attendant discomfort.

Intravenous Effects of Pinaverium Bromide (or Reported) in Cardiac Patients[2]

| | |
|---|---|
| ATRIAL EXCITABILITY | **NO** EFFECT |
| SA CONDUCTION | **NO** EFFECT |
| AV CONDUCTION | **NO** EFFECT |

Open study (2 mg IV and 4 mg IV P.B.) N = 10

Adapted from Guerot C. et al. Electrophysiological study of pinaverium bromide in cardiology. *Current Med. Res. Opinion*, 1988[2]

The spasmolytic effect of Dicetel® has other benefits, too. Through its effects on the colon, Dicetel® can help relieve diarrhea, constipation and bloating alike.[1,3-5] And when the most distressing symptoms of IBS are eased, there may be greater compliance with other parts of the treatment plan.

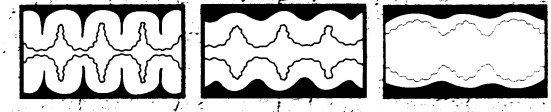
Dicetel® can be prescribed with confidence. Studies have shown no evidence of anticholinergic effects[1,3] or drug interactions.[1,8] Moreover, most side effects reported were infrequent and mild.*

To relieve the pain of IBS, consider Dicetel® 50 mg TID with food and water. Now, an effective drug for spasm is going directly to work in the gut.[1,2,6,7]

For more information, please call the Solvay Medical Information Line 1-800-268-4276.

Dicetel®

PINAVERIUM BROMIDE



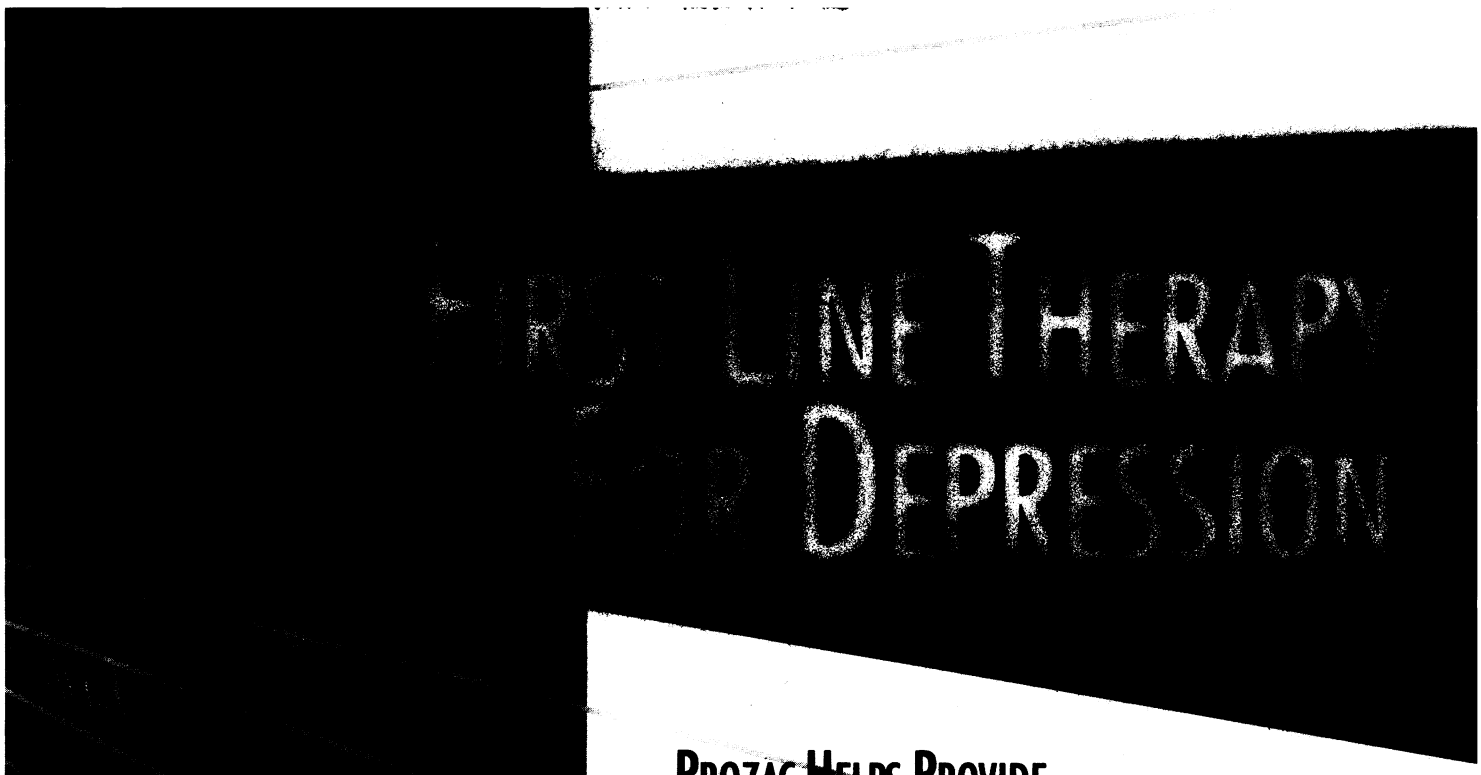
**The GI calcium antagonist**

SOLVAY KINGSWOOD Inc.

PMAC PAAB CCPP

*All side effects have an incidence of less than 1%. The most common of these are minor digestive disorders such as epigastric pain and fullness (0.8%) and nausea (0.5%), which may be related to IBS itself.[1]

For prescribing information see page 1334




## PROZAC HELPS PROVIDE...

- Effective relief from depression[1,2,3] and from the symptoms of anxiety and insomnia associated with depression[4,5]
- Improved compliance with 20 mg capsule, once a day, from start to finish of treatment for many patients[2,6,7]

If you would like to receive:

- More drug information
  OR
- Information on available patient education materials

**Please call 1-800-663-3363 Ext. 16**

PrPROZAC®
fluoxetine hydrochloride

## AS YOUR FIRST LINE OF ACTION

Lilly Eli Lilly Canada Inc.
Scarborough, Ontario

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PAAB
CCPP

1. Feighner JP. J Clin Psych 1985;46:369-372. 2. Altamura AC, Montgomery SA, Wernicke JF. Br J Psych 1988;153(Suppl 3):109-112. 3. Stark P, Hardison D. J Clin Psych 1985;46(3:2):53-58. 4. Cooper GL. Br J Psych 1988;153(Suppl 3):77-86. 5. Beasley CM, Sayler ME, et al. J Clin Psychopharmacol 1991;11(3):166-174. 6. Kaplan HI, Sadock BJ. Pocket Handbook of Clinical Psychiatry. Maryland, Williams & Wilkins, 1990:p. 257-258. 7. Wernicke JF, et al. Psychopharmacol Bull 1987;23(1):164-168.

Calcium Channel Blocker
(dihydropyridine class)


5 mg


10 mg


Now available in **2.5 mg** tablets for dose titration.

*Hypertension in patients over 50 is associated with higher peripheral resistance.*[13] *Plendil acts selectively on the smooth vessel of the vasculature to dilate resistance vessels and lower blood pressure.*[1,2,8]

ONCE • A • DAY

# Plendil®

FELODIPINE EXTENDED RELEASE TABLETS

# VASCULAR SELECTIVE PLENDIL IMPROVES THE SAFETY MARGIN IN HYPERTENSIVE PATIENTS OVER 50.[1,4]

Mild to moderate essential hypertension.*

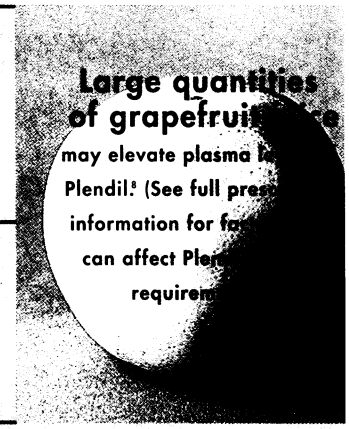
Highly vascular selective calcium channel blocker.[2]

Effective 24 hour blood pressure control.[3]
Enhanced safety margin in patients over 50 who have varying degrees of myocardial dysfunction.[1,4]

Since left ventricular function decreases as part of the normal aging process,[4] cardio-depressant effects are particularly unwanted in most patients over 50. Vascular selectivity results in virtually no effects on cardiac contractility or conduction.[1,2,5]**

Plendil 5 mg OD has been shown to control blood pressure to the same degree as nifedipine PA20 BID and amlodipine 5 mg OD. Also, the tolerability profiles of Plendil and the other dihydropyridines are comparable at these equipotent dosages.[6,7]

Adverse events seen during treatment with Plendil are usually mild and transient, and are generally related to the vasodilatory action of the drug. These include peripheral edema, headache, and feeling of warmth/flushing.[8-11]




Most patients are controlled on the starting dose of 5 mg OD.[6,7] Plendil is also available in 10 mg and 2.5 mg tablets for accurate dose titration. For elderly patients or those with impaired liver function, an initial dose of felodipine 2.5 mg can be considered.[8]

Plendil costs less than virtually all other calcium channel blockers.[12]

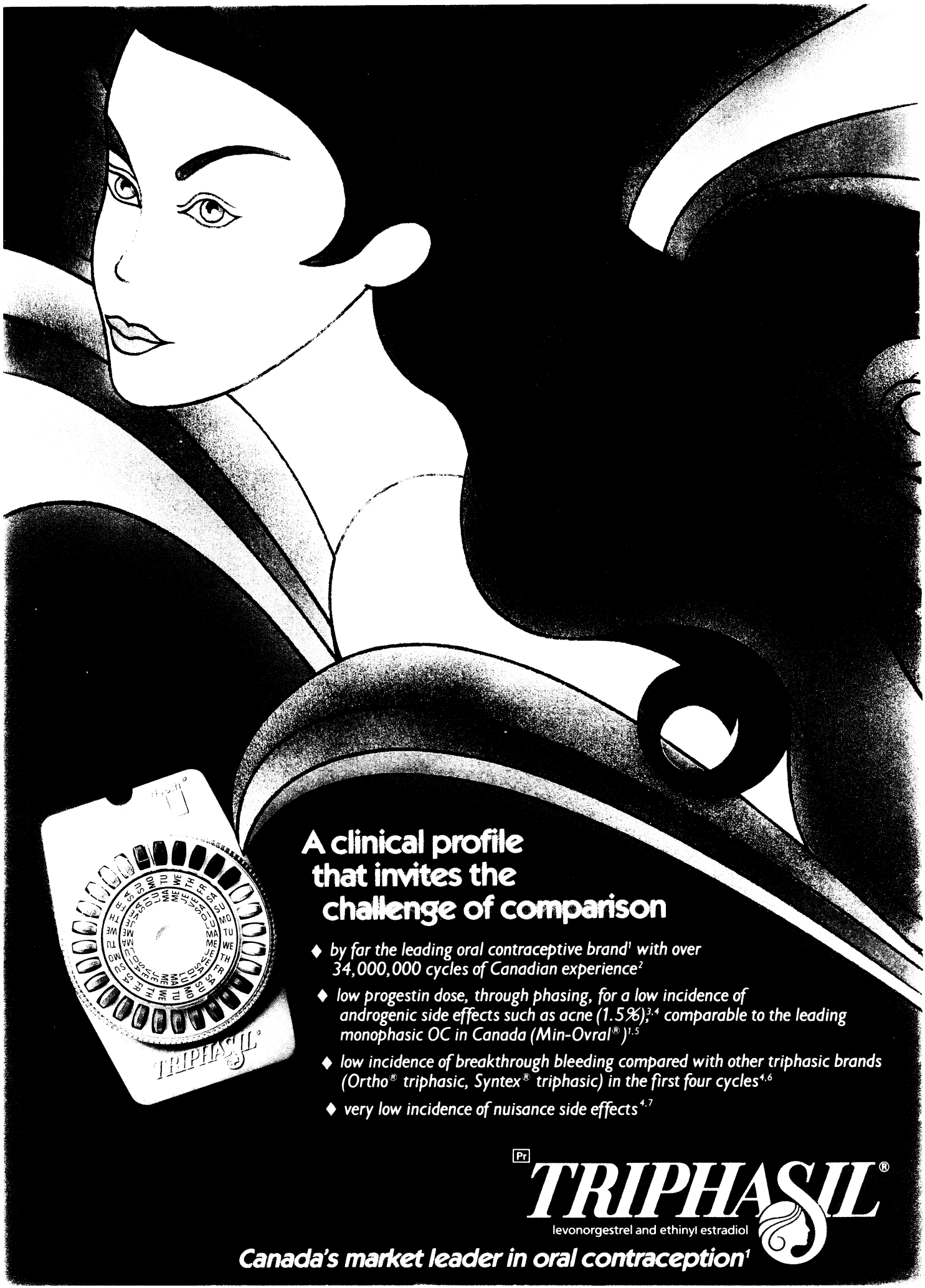
* Should normally be used when a diuretic or beta-blocker is found fo be ineffective or has been associated with unacceptable adverse effects.

** Acute hemodynamic studies in a small number of patients with NYHA Class II and III heart failure treated with felodipine have not demonstrated negative inotropic effects. As with other calcium channel blockers, caution should be exercised when using Plendil in hypertensive patients with compromised ventricular function, particularly in combination with a beta-blocker.

ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

For prescribing information see page 1331




# A clinical profile that invites the challenge of comparison

- *by far the leading oral contraceptive brand[1] with over 34,000,000 cycles of Canadian experience[2]*
- *low progestin dose, through phasing, for a low incidence of androgenic side effects such as acne (1.5%);[3,4] comparable to the leading monophasic OC in Canada (Min-Ovral®)[1,5]*
- *low incidence of breakthrough bleeding compared with other triphasic brands (Ortho® triphasic, Syntex® triphasic) in the first four cycles[4,6]*
- *very low incidence of nuisance side effects[4,7]*

Pr

# TRIPHASIL®

levonorgestrel and ethinyl estradiol

***Canada's market leader in oral contraception[1]***

NOW

# $$EE

THE BENEFITS OF OTHER
HMG-CoA REDUCTASE INHIBITORS

WITHOUT

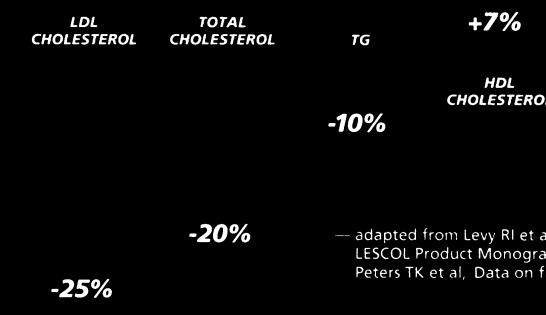
# $EEING

DOUBLE

# INTRODUCING LESCOL

LESCOL, the *only synthetic*[1] HMG-CoA reductase inhibitor, has been developed through a unique and efficient process. This contributes to its significantly lower price. So now you can help patients lower their cholesterol[†] while lowering their costs by about 50%.[2]

LESCOL provides the expected efficacy and safety profiles of the HMG class.[3] It not only lowers LDL cholesterol by 20-25%, but it also positively affects other key lipid parameters.[4,5,6]




— adapted from Levy RI et al, LESCOL Product Monograph,[1] Peters TK et al, Data on file.[2]

And LESCOL is as safe as it is effective, with a safety profile comparable to that of other statins. It is generally well-tolerated, with adverse reactions being mild and transient, occurring at an incidence similar to placebo in controlled clinical trials.[4,5]

Prescribe new LESCOL for your hypercholesterolemic patients and provide highly effective, generally well-tolerated cholesterol control at about half the price. Your patients will thank you for it.

[†]LESCOL is indicated as an adjunct to diet in the treatment of elevated total cholesterol (total C) and LDL-C levels in patients with primary hypercholesterolemia (types IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate.

NEW

℗LESCOL*

FLUVASTATIN SODIUM

LOWERS THEIR CHOLESTEROL
WHILE LOWERING THEIR COST

*co-promoted by*

SANDOZ

SANDOZ CANADA INC.
Dorval, Québec H9R 4P5

ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

*Registered trademark of Sandoz Canada Inc.
Product Monograph available on request
LES-94-03-2539E

MEMBER PAAB PMAC

For prescribing information see page 1350

# "Asthma almost prevented me from doing what I like to do most."

*Robin Hutchinson, Triathlete*

## "A triathlete with asthma? Sounds crazy, but it's true. Before Tilade®, nothing seemed to work.

A few years ago, my doctor prescribed salbutamol on an 'as needed' basis, but it always seemed to wear out. Naturally, my performance suffered. Believe me, there's nothing worse than wheezing during the latter part of a race. Then I went to see Dr. Thomas and he prescribed Tilade® with salbutamol p.r.n. Within two weeks I noticed a huge improvement in my breathing, and I could train longer and harder. My national ranking went from fourteenth to seventh! Thanks to Tilade®, it's definitely not time to retire just yet!"

Tilade® is an effective baseline anti-inflammatory for mild to moderate asthma comparable to low dose inhaled steroids.[1-2]

PLUS it can:

- *provide fast symptom control, usually within one week*[3]
- *control all components of the asthmatic response - bronchospasm, hyperreactivity and inflammation*[4-5]
- *protect against a wide range of triggers (allergic and non-allergic)*[5]
- *control both early asthmatic response (EAR) and late asthmatic response (LAR)*[6-7]

Dr. Thomas: "Robin tells me he is feeling very well on Tilade®. His chest was clear with no wheezes and his $FEV_1$ test was normal. It is clear to me that the addition of Tilade® has allowed him to excel at triathlons and to claim a place on the national team."

FISONS Pharmaceuticals

Fisons Corporation Limited
1851 Sandstone Manor
Pickering, Ontario
L1W 3R9

Tilade® NEDOCROMIL SODIUM
NON-STEROID ANTI-INFLAMMATORY



**This case study does not reflect Tilade's efficacy and tolerability in all patients. Tilade is indicated as adjunctive treatment of mild to moderate asthma.**

Now Available Zostrix-HP

# A hot contender against arthritis pain.

Apply Zostrix directly to affected joints 3 to 4 times daily.[1]

Zostrix contains capsaicin from the hot pepper plant, the only topical agent known to deplete substance P, a major pain transmitter in the arthritic joint.[1,2]

Clinical tests confirm the effectiveness of Zostrix in reducing both pain and inflammation in many arthritis patients.[2,3,4]

When Zostrix was added to existing NSAID regimens, 65% of patients reported additional pain relief.[3]

Zostrix has been shown to significantly reduce pain in arthritis patients with little risk of the side effects of adverse drug interactions associated with oral therapies.[2]

So whether used alone or in adjunct therapy, Zostrix can help your patients put up an effective, targeted fight against arthritis.

**Zostrix®**

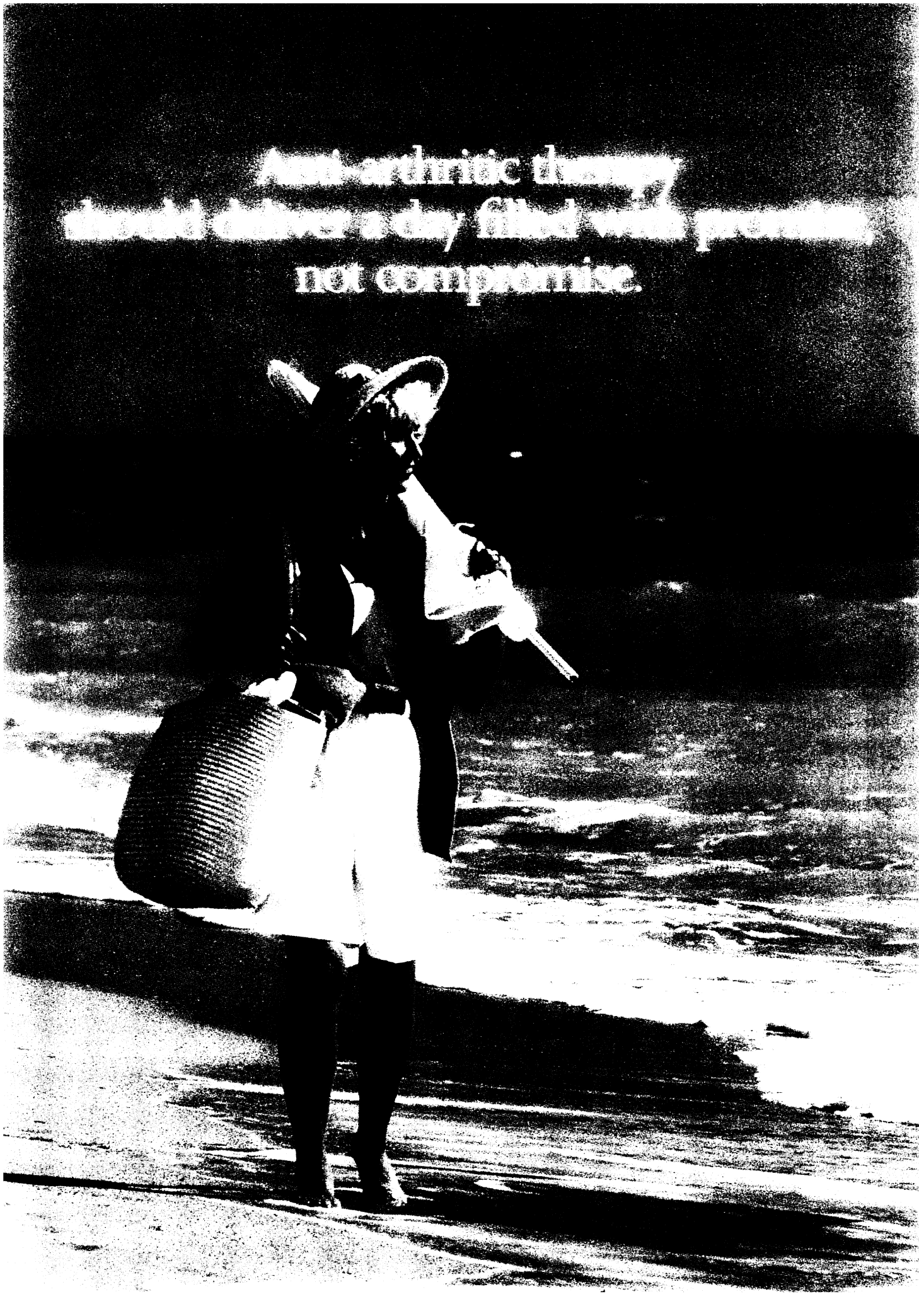
(capsaicin 0.025%)

When it comes to arthritis pain, try fighting fire with fire.

**1-800-661-DERM**
3376

GENDERM

PHYSICIANS' SAMPLE HOTLINE™ 1-800-363-6871



NOW AVAILABLE ON THE ALBERTA FORMULARY

# Disalcid b.i.d.

# Delivering full anti-arthritic efficacy with a reduced risk of severe G.I. effects.

## Significantly lowers the risk of severe G.I. lesions.[1]

New Disalcid (salsalate) reduces the risk of the most severe G.I. lesions associated with NSAID therapies. After three months of therapy, 38% of naproxen patients developed active ulcers or diffuse erosions; no patients receiving Disalcid experienced such severe effects.*[1] In healthy volunteers, Disalcid was associated with a significantly lower incidence of mucosal injury in both the stomach and duodenum than ASA.[2]

Prostaglandins (PG) play a critical role in natural gastric protection.[3] ASA and other NSAID therapies inhibit the synthesis of PG in both platelets and gastric mucosal tissue.[2-5]

Disalcid has little effect on PG synthesis, with significantly less suppression of platelet $PGE_2$ than ASA[4] and no significant changes in $PGE_2$ and $PGF_{2\alpha}$ levels in gastric tissue.[2] (The clinical significance of these findings is not known.)

## Effectively reduces inflammation.

Yet Disalcid offers efficacy comparable to the standard anti-arthritic therapy, ASA, in reduction of joint swelling, pain and morning stiffness.[6] In fact, no other NSAID is more effective in reducing the symptoms of rheumatoid arthritis.

Achieving this efficacy with virtually no effect on PG synthesis[7] challenges classical thinking of the anti-inflammatory process.[2]

New Disalcid. Delivering full anti-inflammatory efficacy and reducing the severe G.I. risks of anti-arthritic therapy.

*The incidence of tinnitus associated with Disalcid is comparable to that of other salicylates.*
*Care should be exercised when Disalcid or other NSAIDs are prescribed for patients with a history of peptic ulcer disease or G.I. bleeding.*

Pr Disalcid™ b.i.d.
(salsalate)

Delivering the efficacy, reducing the severe G.I. risks.

*p<0.01 in rheumatoid arthritis patients (Disalcid 3.0 g/d: n=18; naproxen 750 mg/d: n=21)

Innovation working for you™

**3M Pharmaceuticals**
**3M Canada Inc.**
Post Office Box 5757
London, Ontario N6A 4T1 PAAB

3M

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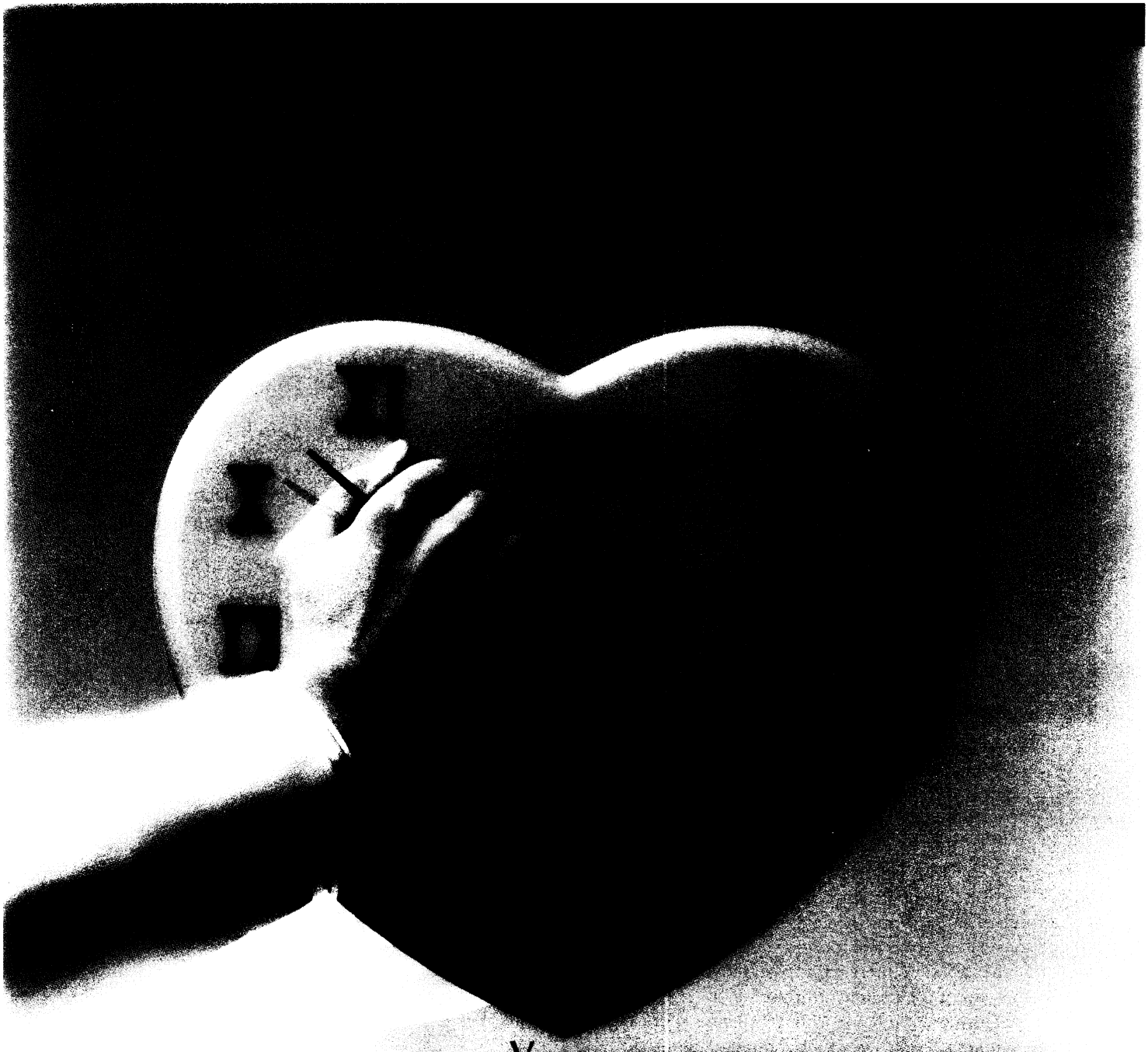


**VASOTEC® is the only ACE inhibitor proven to reduce mortality in congestive heart failure. And by slowing disease progression, VASOTEC® allows more patients to avoid hospitalizations.[1]**

**Adding VASOTEC® to existing diuretic and digoxin therapy may even provide better symptomatic relief for many patients.[2]**

**VASOTEC® can provide effective long-term therapy for heart failure on a once- or twice-a-day dosage.**

**VASOTEC® – for comprehensive treatment of congestive heart failure as adjunctive therapy to digoxin and diuretics.**

MERCK FROSST

**FROSST**
DIV. OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC

℗ VASOTEC

(enalapril maleate tablets, Frosst Std.)

## A vital addition

VASOTEC is the ACE inhibitor documented to prolong ... in clinical trials ...
—CONSENSUS
—V-HeFT II
—SOLVD

BEFORE PRESCRIBING, PLEASE CONSULT ENCLOSED PRESCRIBING INFORMATION

Although VASOTEC is generally well tolerated, the most frequent clinical adverse reactions in controlled clinical trials were: headache (4.8%), dizziness (4.6%) and fatigue (2.8%).

NOT RECOMMENDED DURING PREGNANCY

THIS IS A T[illegible]ANTIHISTAMINE.

IT GOES FROM THE HAND

TO T[illegible]H,

TO THE STOMACH,

INTO THE BLOOD,

TO RECEPTORS ALL OVER

THE BODY

BEFORE IT STARTS WORKING.

# THIS IS A TOPICAL ANTIHISTAMINE.


# IT STARTS WORKING ON CONTACT.[1-4]

## LIVOSTIN* PRESCRIPTION NASAL SPRAY AND EYE DROPS.

It was a simple but brilliant idea. If we could discover a topical antihistamine for allergic rhinitis and conjunctivitis, we would be able to relieve symptoms faster and more effectively. The result. Livostin. An antihistamine so advanced 95% of patients (n=60) treated with it said it was more effective than any therapy they had used ever before.[5] And so fast, it can relieve most allergy symptoms in 3-15 minutes.[6,7]

We know efficacy and speed are not the only measures of a drug. Patients must also be able to live with their therapy. Livostin has a side effect incidence similar to placebo, the most frequent being local irritation.[7] And there is also a very convenient b.i.d. dosage.[7]

For fast relief of allergy symptoms, remember Livostin, because nothing is faster than relief that begins on contact. Livostin is available by prescription only.

**Livostin**
(levocabastine HCl)

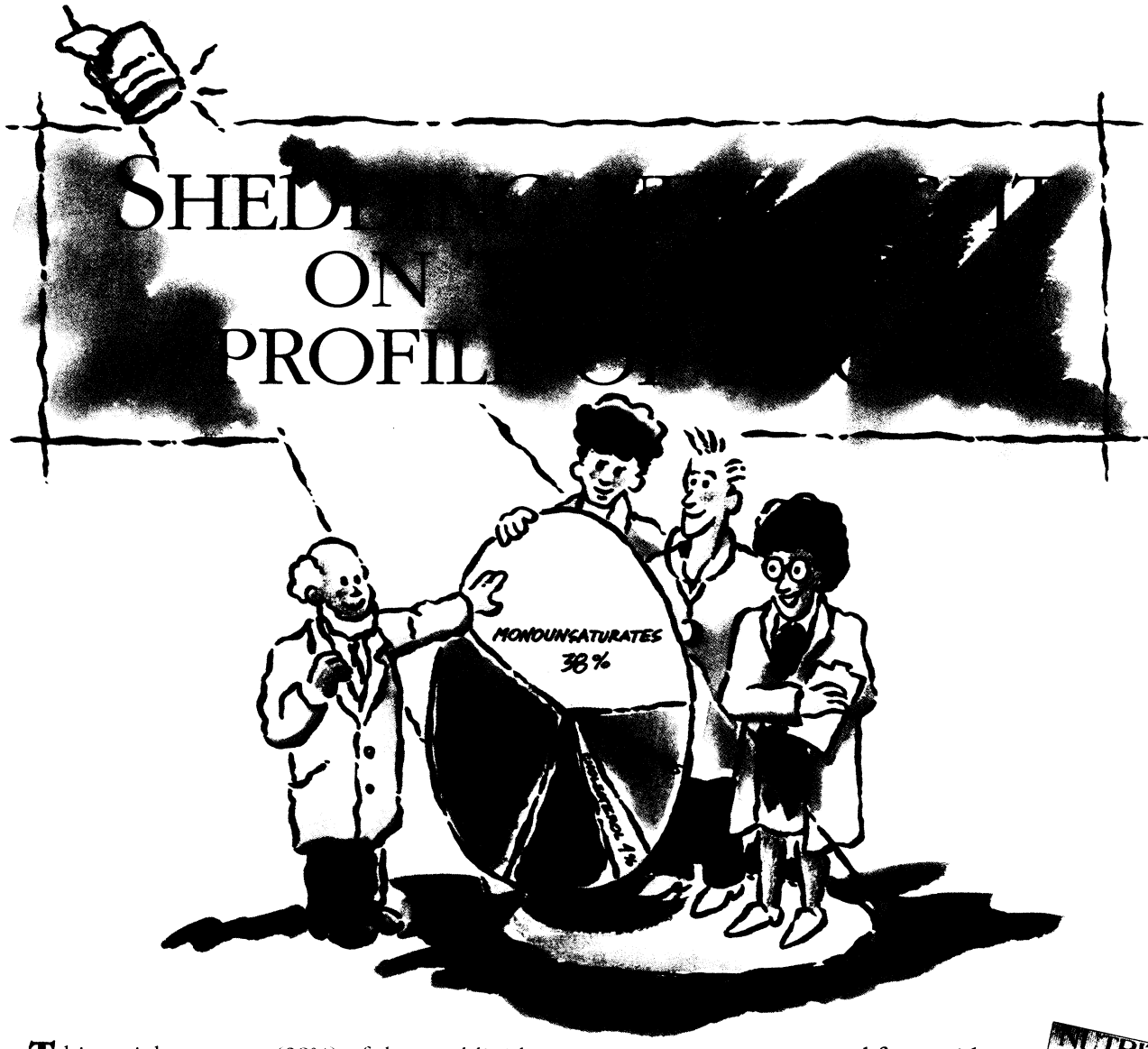
STARTS WORKING ON CONTACT

For prescribing information see page 1338

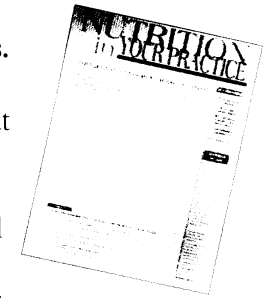
JANSSEN PHARMACEUTICA
Mississauga, Ontario

*Trademark

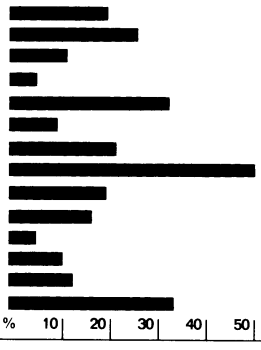
PMAC




**T**hirty-eight percent (38%) of the total lipids in eggs are **monounsaturated fatty acids.** In light of recent studies, this is good news. The net effect of monounsaturates on serum lipids could prove even more positive than that of polyunsaturates since they reduce LDL-cholesterol levels without lowering HDL-cholesterol.[1, 2, 3]




**Nutritional Profile of 2 Large Eggs as % of Recommended Daily Intake of Vitamins and Minerals**




But there's more. An excellent source of several essential nutrients, with as few as 150 kilocalories (623 kilojoules), a serving of two large eggs provides a very high **nutrient density** (see chart).[4]

That's why the newly revised **Canada's Food Guide to Healthy Eating** describes a serving of one to two eggs as part of a healthy and well-balanced diet.[5]

The more light scientists will shed on lipids and their relationship to health, the easier it will be for you to advise your patients. If you wish to learn more on this matter, simply fax us your name and address to (613) 238-1967 to get your free subscription to "Nutrition in Your Practice", an independently reviewed scientific newsletter.

***THE CANADIAN EGG MARKETING AGENCY***
*A RESOURCEFUL PARTNER*
320 Queen St., Suite 1900
Place de Ville, Ottawa, ON K1R 5A3

[1] Grundy SM. Trans-monounsaturated fatty acids and serum cholesterol levels. **N Eng J Med.** 323, 480-81, 1990. [2] Mata *et al.* Effect of dietary monounsaturated fatty acids on plasma lipoproteins in women. **Am J Clin Nutr,** 56, 77-83, 1992. [3] National Institute of Nutrition. Dietary Fats. Fine-tuning the message. **NIN Review,** Winter 1993. [4] Based on **Canadian Nutrient File** data and **Recommended Daily Intakes** as established by Health and Welfare Canada. [5] **Canada's Food Guide to Healthy Eating.** Health and Welfare Canada, 1992.

A serving of two large eggs contains 150 kilocalories (623 kilojoules), 12.5 g protein, 1.2 g carbohydrates, 10.0 g fat, 1.4 g polyunsaturates, 3.8 g monounsaturates, 3.1 g saturates, 432 mg cholesterol and 1.3 g phospholipids.

# NEW BOOKS
•
# VIENT DE PARAÎTRE

## Books for Patients

**Coping with Radiation Therapy: a Ray of Hope**. Daniel Cukier and Virginia E. McCullough. 201 pp. Lowell House, Los Angeles, Calif. 1993. $31.95 (US). ISBN 1-56565-000-X

**Not Like Dad: One Man's Story of Recovery from Incest**. John Andrews. 213 pp. Macmillan Canada, Toronto. 1994. $17.95. ISBN 0-7715-9028-8

**The Radiation Therapy Coloring Book: a Child's Eye View of RT & an Activity Book**. Joi Cangelosi, Tina Miceli, Barbara Siede, Barbara Fineberg. 57 pp. Illust. Ochsner Medical Foundation, New Orleans. 1993. Available free of charge ($12 per dozen shipping and handling) from Center for Radiation Oncology, 1516 Jefferson Highway, New Orleans, LA 70121, USA.

**Self-Medication: Product Information. Volume Two**. 4th ed. Edited by Carmen M.E. Krogh. 452 pp. Illust. Canadian Pharmaceutical Association, Ottawa. 1993. $35 plus $2.50 shipping and handling. ISBN 0-919115-41-1

**That Other Place: a Personal Account of Breast Cancer**. Penelope Williams. 230 pp. Dundurn Press, Toronto. 1993. $14.99. ISBN 1-55002-203-2

## Cardiology

**Arrhythmias**. John A. Kastor. 420 pp. Illust. W.B. Saunders Company/Harcourt Brace & Company, Philadelphia; Harcourt Brace & Company Canada, Inc., Toronto. 1993. $116. ISBN 0-7216-4228-4

## Endocrinology

**Treating Acromegaly: 100 Years On**. Edited by J.A.H. Wass. 211 pp. Illust. Society of Endocrinology, Bristol, England. 1994. $29.95 (US). ISBN 1-898099-05-7

## Ethics

**Physician-Assisted Death**. Edited by James M. Humber, Robert F. Almeder, Gregg A. Kasting. Biomedical Ethics Reviews series; editors, James M. Humber and Robert F. Almeder. 150 pp. Humana Press, Totowa, NJ. 1994. $39.95 (US). ISBN 0-896-03265-5

## Health care

**Quest for Quality in Canadian Health Care: Continuous Quality Improvement**. 141 pp. Illust. Health Services Directorate, Health Service Systems Division, Health Canada, Ottawa. 1993. Price not stated. ISBN 0-662-21173-1

**Shifting Sands: Government–Group Relationships in the Health Care Sector**. Joan Price Boase. Canadian Public Administration Series; editors, Iain Gow and Paul Pross. 207 pp. McGill–Queen's University Press, Montreal. 1994. $34.95. ISBN 0-7735-1158-X

## Miscellaneous

**Clinical Detective Stories: a Problem-Based Approach to Clinical Cases in Energy and Acid–Base Metabolism**. Mitchell L. Halperin and Francis S. Rolleston. 295 pp. Illust. Portland Press, Chapel Hill, NC. 1993. $42.95. ISBN 1-85578-999-X

**How to Write A Paper**. Edited by George M. Hall. 112 pp. Illust. BMJ Publishing Group, London. 1994. 11£. ISBN 0-7279-0822-7

**Life, Death and Aid: the Médecins Sans Frontières Report on World Crisis Intervention**. Edited by François Jean. 160 pp. Illust. Médecins Sans Frontières; Routledge, New York. 1993. Price not stated. ISBN 0-415-10550-1

**Medical Staff Credentialing: a Practical Guide**. Fay A. Rozovsky, Lorne E. Rozovsky, Linda M. Harpster. 120 pp. Illust. American Hospital Publishing, Inc., Chicago. 1994. $49 (US). ISBN 1-55648-112-8

**Publication Peer Review: an Annotated Bibliography**. Compiled by Bruce W. Speck. 252 pp. Greenwood Press, Westport, Conn. 1993. $65 (US). ISBN 0-313-28892-5

**Treatment of the Chemically Dependent Homeless: Theory and Implementation in Fourteen American Projects**. Edited by Kendon J. Conrad, Cheryl I. Hultman, John S. Lyons. 246 pp. Illust. Haworth Press, Inc., New York. 1993. $49.95 (US), hardcover; $29.95 (US), paperback. ISBN 1-56024-476-3, hardcover; 1-56024-525-5, paperback. Also published as *Alcoholism Treatment Quarterly*, 1993; 1 (3 and 4).

## Pediatrics

**Nelson Textbook of Pediatrics: Pocket Companion**. Richard E. Behrman and Kenneth H. Webb. 482 pp. Illust. W.B. Saunders Company/Harcourt Brace & Company, Philadelphia; Harcourt Brace & Company Canada, Inc., Toronto. 1993. $26.95. ISBN 0-7216-3968-2

## Pharmacology

**Pharmacology and Therapeutics in Respiratory Care**. Theodore J. Witek, Jr., and E. Neil Schachter. 444 pp. Illust. W.B. Saunders Company/Harcourt Brace and Company, Philadelphia; W.B. Saunders Company Canada Limited, Toronto. 1994. $54.50. ISBN 0-7216-3483-4

**Pharmacology for Prehospital Emergency Care**. 2nd ed. Richard K. Beck. 292 pp. Illust. F.A. Davis Company, Philadelphia. 1994. $22.95 (US). ISBN 0-8036-0692-3

## Physiology

**Oxygen Transport: Principles and Practice**. Edited by J. Denis Edwards, William C. Shoemaker, Jean-Louis Vincent. 359 pp. Illust. W.B. Saunders Company Ltd., Philadelphia; Harcourt Brace & Company Canada, Inc. Toronto. 1993. $81. ISBN 0-7020-1576-8

## Sexually Transmitted Disease

**A Comprehensive Guide for the Care of Persons with HIV Disease. Module 1: Adults — Men, Women, Adolescents.** Edited by Moira Tobin, F.J. Chow, Ian Bowmer, Gerry Bally. 96 pp. Illust. College of Family Physicians of Canada, Mississauga, Ont. 1993. Price not stated. ISBN 0-921413-53-X

## Soins palliatifs

**Les Annales de soins palliatifs : Douleur et antalgie**. Collection Amaryllis, no$^2$. David J. Roy et Charles-Henri Rapin. 187 pp. Illust. Centre de bioéthique, Institut de recherches cliniques du Montréal, Montréal. 1993. 30 $. ISBN 2-9802538-2-0

## Sports Medicine

**Oxford Textbook of Sports Medicine**. Edited by Mark Harries, Clyde Williams, William D. Stanish, Lyle J. Micheli. 714 pp. Illust. Oxford University Press Canada, Toronto. 1994. $129.95. ISBN 0-19-262009-6

## Urology

**Benign Prostatic Hyperplasia: Diagnosis & Treatment**. Benign Prostatic Hyperplasia Guideline Panel. *Clinical Practice Guidelines* (AHCPR publ. 94-0582), 215 pp. Illust. *Quick Reference Guide for Clinicians* (AHCPR 94-0583), 13 pp. Illust. *Treating Your Enlarged Prostate* (AHCPR publ. 94-0584), 21 pp. Illust. Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, Rockville, Md. 1994. Available at no charge from AHCPR Publications Clearinghouse, PO Box 8547, Silver Spring, MD 20907, USA.

# Selection ❖ ❖ Sélection

## Strengthening the Foundation: The Role of the Physician in Primary Health Care in Canada

Primary medical care is first-contact, continuing, coordinated and comprehensive. It includes diagnosis, treatment and management; prevention and health promotion; ongoing support; and family and community intervention, when needed.

*Strengthening the Foundation* is an example of the CMA working for you — and for all Canadians. Canada's health care system is under intense scrutiny by both provincial and territorial governments. Primary health care delivery is one of their targets, modification of the methods for this delivery is one of their goals. The medical community must convey to these governments its recommendations on ways in which primary medical care, through the patient's own family physician, can *strengthen* health care delivery in Canada. *Strengthening the Foundation* is our vehicle for accomplishing this goal — *our* goal.

Publication of this document was accomplished by a working group representing the CMA, the College of Family Physicians of Canada, the Royal College of Physicians and Surgeons of Canada, and the Canadian Association of Internes and Residents. A cross-Canada survey of key informant organizations was conducted in December 1992, followed by an extensive review, consultations and a survey of delegates at CMA's General Council meeting in August 1993. Recognizing both the urgency and importance of this matter, the working group produced *Strengthening the Foundation* in less than a year.

How can physicians help? There are 31 recommendations in this document. Primary medical care *can* adapt to the changing times. Family physicians can refine their expertise through continuing education, research and quality improvement initiatives. They can meet the challenge to remain accessible to their patients and, when necessary, improve continuity of care. This is the profession's challenge.

## Consolider la base : le rôle du médecin dans les soins de santé primaires au Canada

Les soins médicaux primaires sont des soins de premier contact, continus, coordonnés et complets. Ils comprennent le diagnostic, le traitement et la gestion de cas, la prévention de la maladie et la promotion de la santé, de même que l'appui courant, avec intervention des membres de la famille et de la communauté au besoin.

*Consolider la base* témoigne des efforts que l'AMC déploie pour vous — et pour tous les Canadiens. Les gouvernements provinciaux et territoriaux scrutent à la loupe le système de soins de santé du Canada. La prestation des soins de santé primaires constitue une de leurs cibles et la modification des modes de prestation de ces soins, un de leurs buts. Les milieux médicaux doivent recommander à ces gouvernements des façons dont les soins médicaux primaires fournis par le médecin de famille du patient peuvent consolider la prestation des soins de santé au Canada. *Consolider la base* est notre moyen d'atteindre ce but — *notre* but.

Ce document a été publié par un groupe de travail constitué de représentants de l'AMC, du Collège des médecins de famille du Canada, du Collège royal des médecins et chirurgiens du Canada et de l'Association canadienne des internes et des résidents. On a procédé à une enquête nationale auprès d'organisations clés en décembre 1992, puis à une étude détaillée et à des consultations auprès des délégués au Conseil général de l'AMC, en août 1993. Reconnaissant l'urgence et l'importance de la question, le groupe de travail a produit *Consolider la base* en moins d'un an.

Comment les médecins peuvent-ils aider? Le document contient 31 recommandations. Les soins médicaux primaires *peuvent* s'adapter au changement. Les médecins de famille peuvent se perfectionner par l'éducation continue, la recherche et l'amélioration de la qualité. Ils peuvent relever le défi de demeurer accessibles pour leurs patients et, au besoin, améliorer la continuité des soins. Voilà le défi que doit relever la profession.

# CHANGE THE GUARD

INTRODUCING

# PrALTACE® ramipril

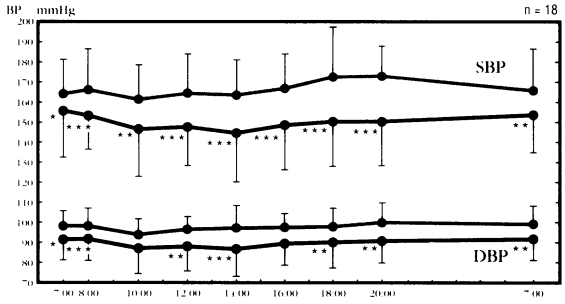
# ON GUARD FOR HYPERTENSIVES

*"Their [ACE inhibitors] mechanism of action is considered to be due, in part, to an inhibition of ACE in the plasma and in the local tissue..."*[1] *Erman A, et al.*

## EXCLUSIVE HUMAN DATA CONFIRMS MARKED PLASMA AND TISSUE ACE INHIBITION[1,2]

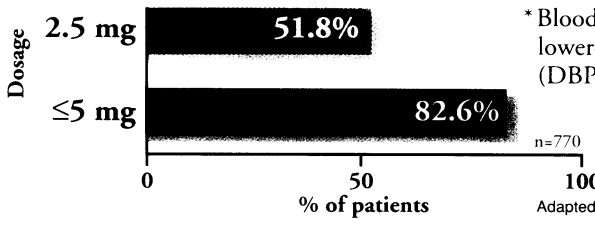
*"...[with Altace] a better tissue penetration and a more pronounced local ACE inhibition in the target organs has been observed [in animals], as compared to other ACE inhibitors."*[2] *Bender N, et al.*

## 24-HOUR BLOOD PRESSURE CONTROL[3]



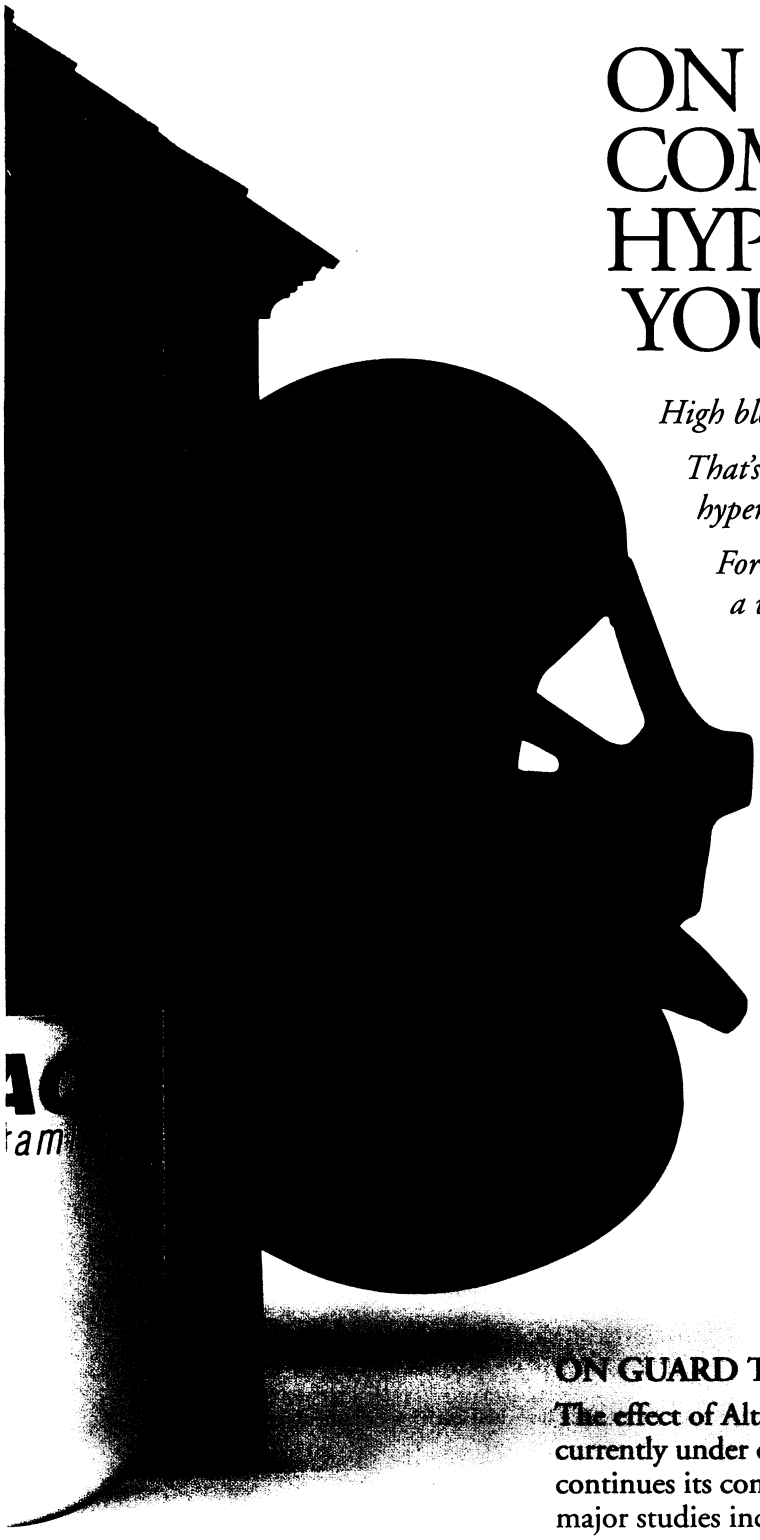

Adapted from Kaneko, et al.

## HIGH RESPONDER RATE AT LOW DAILY DOSE WITH ALTACE*[4]




*Blood pressure lowered to normal (DBP ≤ 90 mmHg)

Adapted from Carré, et al.



# ON GUARD WHEN COMPLICATIONS OF HYPERTENSION ARE YOUR CONCERN

*High blood pressure is a major cause of end-organ damage.*[5-7]

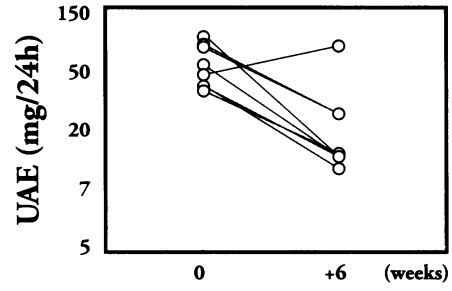
*That's why antihypertensive action can reduce the risk of hypertension-induced damage to organs.*[7]

*For example, in the kidney, Altace provides protection for a variety of hypertensive patient types.*[8-10]

## RENOGUARD

In general, with Altace renal function will not deteriorate and may improve.[8-12]

***Preservation of renal function, even at low dose - beneficial for hypertensive diabetics****[8]




** 75% reduction of albuminuria in normotensive diabetics.*
Adapted from Marre, et al.

## ON GUARD THROUGH CARDIOVASCULAR RESEARCH

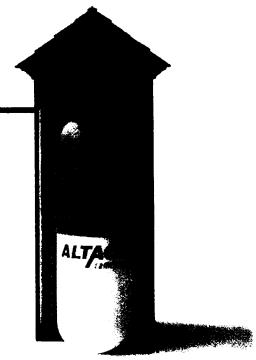
**The effect of Altace** on LVH, atherosclerosis and other risk factors is currently under clinical investigation. Hoechst-Roussel Canada Inc. continues its commitment to cardiovascular research by supporting major studies including the AIRE, HEART, HOPE and SECURE trials.

*BODYGUARD FOR HYPERTENSIVES*

**ALTACE®**
ramipril

INTRODUCING

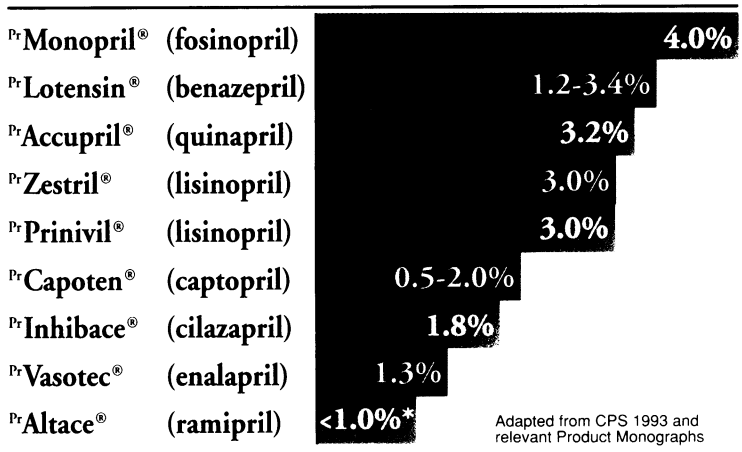
# PrALTACE® ramipril



# ON GUARD WITH VERY WELL TOLERATED THERAPY

## LOW INCIDENCE OF COUGH

*(% of cough among ACE inhibitors)* [13]

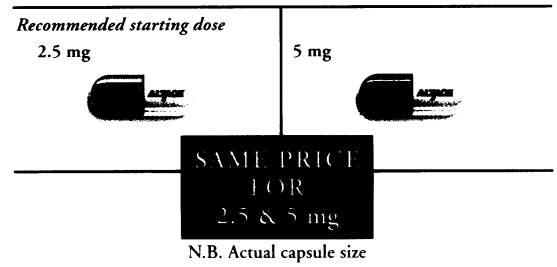



Adverse reactions/discontinuations reported in product monographs are from different data bases and may not be predictive of comparative rates.

* In one later study, increased cough was seen in almost 12% of patients.

## HIGH RESPONDER RATE

*(>80% of patients at doses ≤ 5 mg/OD)* [4]




N.B. Actual capsule size

## DUAL ROUTE OF ELIMINATION: AN EXTRA SAFETY FACTOR

***Dosage may need to be reduced for renally impaired patients.*** [11]

## ON GUARD FOR HYPERTENSIVES

- High, sustained plasma and tissue-ACE inhibition
- 24-hour efficacy at low dose
- A judicious choice when hypertension-induced end-organ damage is your concern
- Helps prevent deterioration of renal function
- Convenient once-daily dosage
- Excellent tolerability profile
- Low incidence of cough
- Same low price for 2.5 and 5 mg

Altace is indicated in the treatment of essential hypertension, normally when beta-blockers or diuretics are inappropriate.

Recommended starting dose is 2.5 mg/OD. Usual dosage range is 2.5 - 10 mg/daily. For renally impaired patients or patients already on diuretics, initial dose is 1.25 mg/daily.

Maximum dose is 20 mg/daily.

Like other ACE inhibitors, Altace is not recommended for pregnant or lactating women and should be used with caution in patients with renal insufficiency.

Product Monograph available upon request.

**Hoechst-Roussel Canada Inc.**
ADAL 08/94

MEMBER PMAC PAAB

uation of the diuretic and/or ALTACE may be required.

**Anaphylactoid reactions during membrane exposure:** Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

**Anaphylactoid reactions during desensitization:** There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

**Hyperkalemia and Potassium-Sparing Diuretics:** Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

**Surgery/anesthesia:** In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume replection.

**Aortic Stenosis:** There is concern, on theoretical grounds, that patients with aortic stenosis might be [illegible] risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

**Patients with Impaired Liver Function:** Hepatitis (hepatocellular and/or cholestatic), elevation of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing hepatic abnormalities. In most cases the changes were reversible upon discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first several months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate.

There are no adequate studies in patients with hepatic and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing hepatic abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and dose monitoring of response and metabolic effects should apply.

**Nursing Mothers:** Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

**Pediatric Use:** The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

**Use in Elderly:** Although clinical experience has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism).

**Patient alertness:** ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

**Cough:** A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

**Drug interactions: Concomitant Diuretic Therapy:** Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of hypotensive effects after the first dose of ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If it is not possible to discontinue the diuretic, the starting dose of ALTACE should be reduced and the patient should be closely observed for several hours following the initial dose and until blood pressure has stabilized (see WARNINGS and DOSAGE AND ADMINISTRATION).

**Agents Increasing Serum Potassium:** Since ALTACE decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.

**Agents Causing Renin Release:** The antihypertensive effect of ALTACE is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

**Lithium:** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be further increased.

**Antacids:** In one open-label, randomized, cross-over single dose study in 24 male subjects, it was determined that the bioavailability of ALTACE and the pharmacokinetic profile of ramiprilat were not affected by concomitant administration of the antacid, magnesium and aluminum hydroxides.

**Digoxin:** In one open-label study in 12 subjects, administered multiple doses of both digitoxin and digoxin (Lanoxin®), no changes were found in digoxin, ramiprilat, and digitoxin.

Ace[illegible] dose[illegible] ace[illegible] con[illegible] patients [illegible] ber[illegible] time[illegible] observed. No [illegible] sive [illegible] concomi[illegible] tant admini[illegible] nflammatory [illegible]

**ADVERSE REACTIONS: ALTACE** (ramipril) has been evaluated clinically in over 4,000 hypertensive patients. Almost 700 elderly patients have participated in controlled trials. Long-term safety has been assessed in almost 700 patients treated for 1 year or more. There was no increase in the incidence of adverse events in elderly patients versus the same daily dose. The overall frequency of adverse events was not related to duration of therapy or total daily dose.

Serious adverse events occurring in North American controlled clinical trials with ALTACE monotherapy in hypertension (n=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); angina pectoris (0.3%); syncope (0.1%). Among all North American ALTACE patients (n=1244), angioedema occurred in 0.3% of patients treated with ALTACE and a diuretic (0.1%).

The most frequent adverse events occurring in North American placebo-controlled clinical trials with ALTACE monotherapy in hypertensive patients (n=65[illegible]) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); pruritus (1.1%); dyspnea (1.1%). Discontinuation of therapy in clinical adverse events was required in 5 patients (0.8%).

In placebo-controlled trials, an excess of upper respiratory infections and flu syndrome was seen with the ramipril group; these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1 year study, cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (n=972) have required discontinuation because of cough.

Clinical adverse events occurring in less than 1% of patients treated with ALTACE in controlled clinical trials, or since in post-marketing experience, are listed below by body system:

**Body as a whole:** anaphylactoid reactions, allergic edema.

**Cardiovascular:** symptomatic hypotension, syncope, angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, cerebrovascular disorders.

**CNS:** anxiety, amnesia, convulsions, increased cough, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, vision disturbances.

**Dermatologic:** apparent hypersensitivity reactions (manifested by dermatitis, pruritis, or rash, with or without fever), photosensitivity, purpura.

**Gastrointestinal:** abdominal pain, pancreatitis, anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, nausea, increased salivation, taste disturbance, vomiting.

**Renal:** increases in blood urea nitrogen (BUN) and serum creatinine.

**Other:** arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, weight gain.

**Clinical laboratory test findings:** increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; leukopenia, eosinophilia, proteinuria.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** No data are available regarding overdosage of ALTACE (ramipril) in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion with normal saline. It is not known if ramipril or ramiprilat can be removed from the body by hemodialysis.

**DOSAGE AND ADMINISTRATION:** Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

**Monotherapy:** The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

**Concomitant Diuretic Therapy:** Symptomatic hypotension [illegible] occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

**Use in renal impairment:** For patients with a creatinine clearance below 40 mL/min/1.73 m² (serum creatinine above [illegible] mg/dL), the recommended initial dose is 1.25 mg ALTACE [illegible] dosage may be increased upward until adequate [illegible] maximum total daily dose [illegible] impairment (creatinine clearance [illegible] mL/min) the maximum dose of [illegible] mg/d.

[illegible] is available in size no. [illegible] ving potencies (colors [illegible]

[illegible] mg (white [illegible] ated with "ALTACE"; [illegible] opaque cap, [illegible] 2.5").

[illegible] mg (white [illegible] with "ALTACE"; [illegible] range opaque [illegible] h "2.5").

[illegible].0 mg [illegible] printed with "ALTACE"; red opaque [illegible] 5").

• 10 [illegible] printed with "ALTACE"; [illegible] with "10").

ALTACE capsules 1.25 mg, 2.5 mg, 5.0 mg and 10 mg are packaged in [illegible] (4 x 7 blister-packed) capsules.

Product monograph available upon request.

**REFERENCES : 1.** Erman A, et al. J Hypertens 1991; 9:1057-1062. **2.** Bender N, et al. Clin Physiol Biochem 1992: 9:105-112. **3.** Kaneko Y, et al. Am J Cardiol 1987; 59:86D-91D. **4.** Carré A, et al. Clin Physiol Biochem 1992; 9:105-112. **5.** Francis CK. Am J Med 1990; 88(3):3S-8S. **6.** Frohlich ED, et al. NEJM 1992; 327(14): 998-1008. **7.** Houston MC. Am Heart J 1992; 1337-1367. **8.** Marre M, et al. J Cardiovasc Pharmacol 1991; 18(2):S165-S168. **9.** Schreiner M, et al. J Cardiovasc Pharmacol 1991; 18(2): S137-S140. **10.** Hirata Y, et al. Cur Ther Research 1990; 45(6):967-974. **11.** Altace Product Monograph. **12.** Al Nahhas AM, et al. Nephron 1990; 54:47-52. **13.** CPS 1993 and relevant Product Monographs.

**ALTACE®** ramipril

ADAL 08/94

**Hoechst-Roussel Canada Inc.**
Montreal, Quebec

MEMBER PMAC PAAB

# Pr ALTACE® ramipril

Capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg

**PHARMACOLOGIC CLASSIFICATION:** Angiotensin Converting Enzyme Inhibitor

**ACTION AND CLINICAL PHARMACOLOGY:** ALTACE (ramipril) is an angiotensin converting enzyme (ACE) inhibitor, which is used in the treatment of essential hypertension.

Following oral administration, ALTACE is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

Angiotensin-converting enzyme catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE activity leads to decreased levels of angiotensin II thereby resulting in decreased vasoconstriction and decreased aldosterone secretion. The latter decrease may result in a small increase in serum potassium (see PRECAUTIONS). Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal renin secretion result in increases in plasma renin activity. ACE is identical to kininase II. Thus, ramipril may also block the degradation of the vasodepressor peptide bradykinin, which may contribute to its therapeutic effect.

While the mechanism through which ALTACE lowers blood pressure appears to result primarily from suppression of the renin-angiotensin-aldosterone system, ALTACE has an antihypertensive effect even in patients with low-renin hypertension. Although ALTACE was antihypertensive in all races studied, it was somewhat less effective in blacks than in nonblacks.

**Pharmacokinetics and Metabolism:** Following oral administration, ramipril is rapidly absorbed with peak plasma concentrations occurring within 1 hour. The extent of absorption of ramipril is 50-60% and is not significantly altered by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced. Following absorption, ramipril is rapidly hydrolyzed in the liver to its active metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat is 56%.

Ramipril is almost completely metabolized to the active metabolite ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ALTACE, about 60% of the parent drug and its metabolites is excreted in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Plasma concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the recommended dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44% respectively when 5 mg of oral ramipril was compared to 5 mg given intravenously. Plasma concentrations of ramiprilat decline in a triphasic manner. The initial rapid decline, which represents distribution of the drug, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase has a half-life of 9-18 hours, and the terminal elimination phase has a prolonged half-life of > 50 hours. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations was 13-17 hours, but was considerably prolonged at 2.5 mg (27-36 hours).

After once daily dosing, steady state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are higher than those seen after the first dose of ALTACE especially at low doses (2.5 mg). In patients with creatinine clearance < 40 mL/min/1.73m², increases in Cmax and AUC of ramipril and ramiprilat compared to normal subjects were observed following multiple dosing with 5 mg ramipril (see DOSAGE AND ADMINISTRATION).

In patients with impaired liver function, plasma ramipril levels increased about 3-fold, although peak concentrations of ramiprilat in these patients were not different from those seen in patients with normal hepatic function.

A single dose pharmacokinetic study conducted in a limited number of elderly patients indicated that peak ramiprilat levels and the AUC for ramiprilat are higher in older patients (see PRECAUTIONS).

**Pharmacodynamics:** Administration of ALTACE to patients with mild to moderate essential hypertension results in a reduction of both supine and standing blood pressure usually with little or no orthostatic change or change in heart rate. Symptomatic postural hypotension is infrequent, although this may occur in patients who are salt- and/or volume-depleted (see WARNINGS).

In single dose studies, doses of 5-20 mg of ALTACE lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. At recommended doses given once daily, antihypertensive effects have persisted over 24 hours.

The effectiveness of ALTACE appears to be similar in the elderly (over 65 years of age) and younger adult patients given the same daily doses.

In studies comparing the same daily dose of ALTACE given as a single morning dose or as a twice daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

The antihypertensive effect of ALTACE and thiazide diuretics used concurrently is greater than that seen with either agent used alone.

Abrupt withdrawal of ALTACE has not resulted in rapid increase in blood pressure.

**INDICATIONS AND CLINICAL USE:** ALTACE (ramipril) is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics.

In using ALTACE, consideration should be given to the risk of angioedema (see WARNINGS).

ALTACE should generally be withheld for patients in whom treatment with ... on a ... was found ineffective or poorly tolerated because of adverse effects.

ALTACE can also be ... in those patients in whom ... are contraindicated ... conditions in which these ... adverse effects.

The safety and efficacy of ALTACE in ... and renovascular hypertension have not been established and therefore, its use in these conditions is not recommended.

The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

**When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy, and INFORMATION FOR THE PATIENT).**

**CONTRAINDICATIONS:** ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or to other patients who have a history of angioedema.

**WARNINGS: Angioedema:** Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

**Hypotension:** Symptomatic hypotension has occurred after administration of ALTACE, usually after the first dose and dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered.

**Neutropenia/agranulocytosis:** Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

**Use in Pregnancy:** ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

In rare cases (probably less than one in every thousand pregnancies) in which no alternative to ACE inhibitor therapy will be found, the mother(s) should be apprised of the potential hazard(s) to their fetus(es). Serial ultrasound examinations should be performed to assess fetal development and well-being and the volume of amniotic fluid.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered life-saving for the mother. A non-stress test (NST), and/or a biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. If concerns regarding fetal well-being still persist, a contraction stress testing (CST) should be considered. Patients and physicians should be aware, however, that oligohydramnios may not appear until the fetus has sustained irreversible injury.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. It is not known if ramipril or ramiprilat can be removed from the body by hemodialysis.

It is not known whether exposure limited to the first trimester of pregnancy can adversely affect fetal outcome. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contracture, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to ACE inhibitor exposure.

Animal ... of ramipril were seen in studies of pregnant ... synomolgus monkeys. The doses used were ... 1000 mg/kg in rats (2500 times maximum ... 1.0, or 2.5 mg/kg in rabbits (6.25 times ... human dose), and 5, 50, or 500 mg/kg in ... (1250 times maximum human dose). In rats, the highest dose caused reduced food intake in the dams, with consequent reduced birthweights of the pups and weight development during the lactation period. In rabbits, maternal effects were mortalities (high and middle dose) and reduced body weight. In monkeys, maternal effects were mortalities (high and middle dose), vomiting, and reduced weight gain.

**PRECAUTIONS: Renal Impairment:** Renal function should be assessed before initiating therapy with ALTACE (ramipril).

ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

In patients with severe heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients renal function should be closely monitored.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea nitrogen and creatinine especially when ALTACE has been given concurrently with a diuretic. Dosage reduction and/or discontin-

# INTRODUCING A NEW
# ON A SCALE OF 1

## TWICE·A·DAY TO TREAT

A new way to treat G.I. pain and associated symptoms.[1,2] The 20 mg tablet, twice-a-day.

Promotes compliance, helps maximize efficacy,[3] and gets to the underlying cause of those symptoms acid suppressing therapies don't treat.[4]

Shown to be as well tolerated as ranitidine 150 mg b.i.d.[5]

## ONCE·A·DAY TO PREVENT

An effective way to help prevent relapse.[6] The 20 mg tablet, once-a-day.

Proven to prevent relapse in patients with chronic, recurrent reflux.[6]

And more effective than $H_2$ therapy.[†,††,4,6-8]

**Prepulsid 20 mg is indicated for the relief of heartburn, regurgitation, epigastric pain, bloating, postprandial fullness and early satiety due to gastroesophageal reflux

NEW 20 mg

# PREPULSID TABLET. TO 10, IT'S A 20.

RELIEVING MORE THAN JUST PAIN BY RESTORING DIGESTIVE MOVEMENT.

**Prepulsid*** CISAPRIDE **20mg**

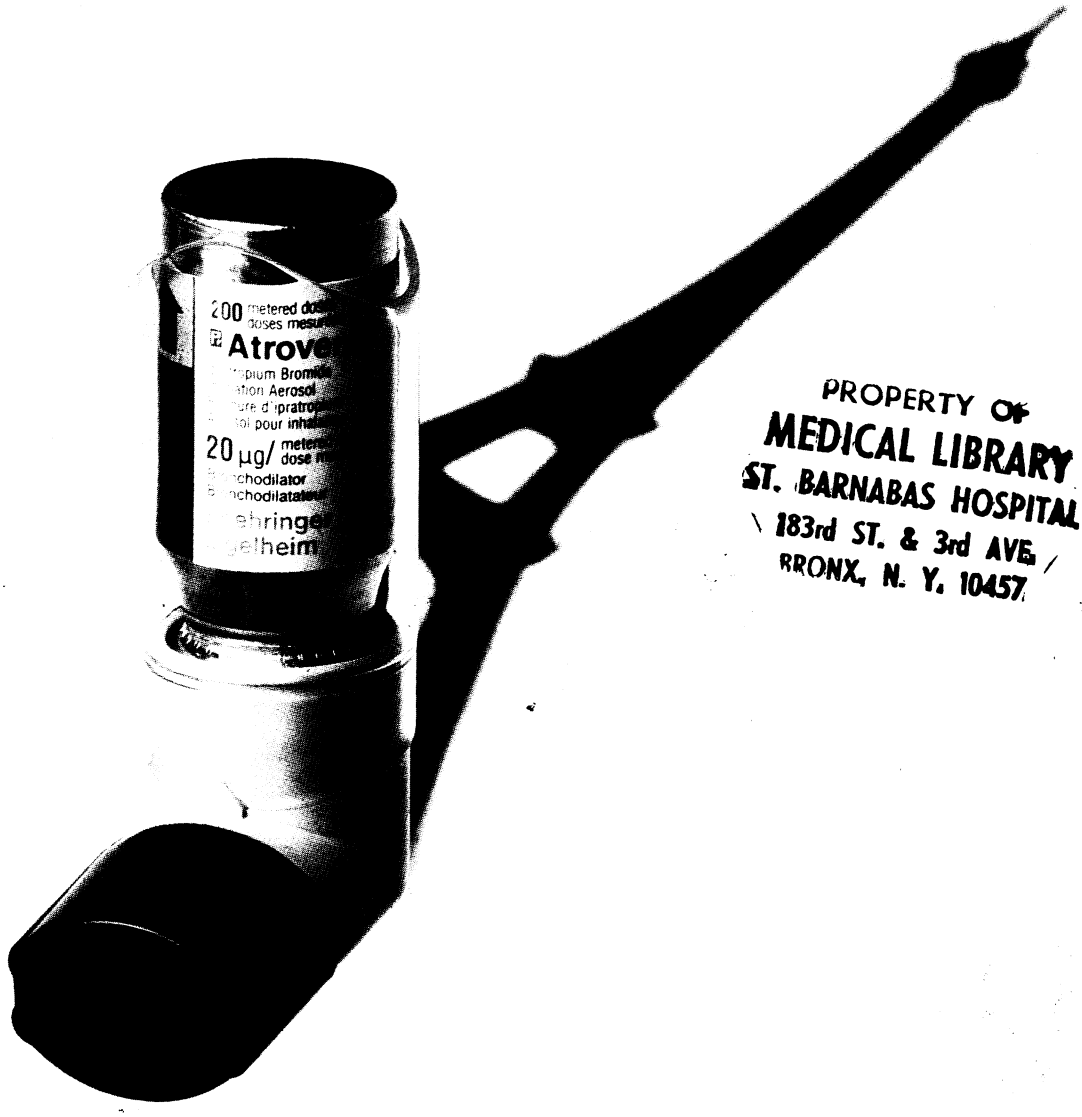
*Trademark

JANSSEN PHARMACEUTICA Mississauga, Ontario

disease. † Ranitidine, cimetidine †† $H_2$ therapy is not indicated for prophylaxis or maintenance in GERD.

For prescribing information see page 1337

# ONE AND ONLYs






**Just as the Eiffel Tower is a landmark in architecture because of its unique design... Atrovent Inhaler is a landmark in COPD bronchodilation because of its unique anticholinergic action**

"All or much of the achievable reversibility of airway obstruction in emphysema is due to inhibition of cholinergic airway tone... ."[1]

**In COPD patients, Atrovent Inhaler can provide superior bronchodilation[2-4] and fewer side effects than a beta$_2$ agonist[3]**

"Ipratropium [Atrovent] produced a significantly greater improvement than albuterol [salbutamol] in the $FEV_1$ at 30 minutes and at 3, 4 and 5 hours and in the forced vital capacity at one through six hours."[2]

**"Guidelines for the assessment and management of chronic obstructive pulmonary disease" confirms...**

"In most patients who have COPD, inhaled quaternary anticholinergic agents offer bronchodilatation at least equal to and often greater than that seen with $\beta_2$ agonists and produce fewer side effects."[5]

**Canadian Thoracic Society Workshop Group**

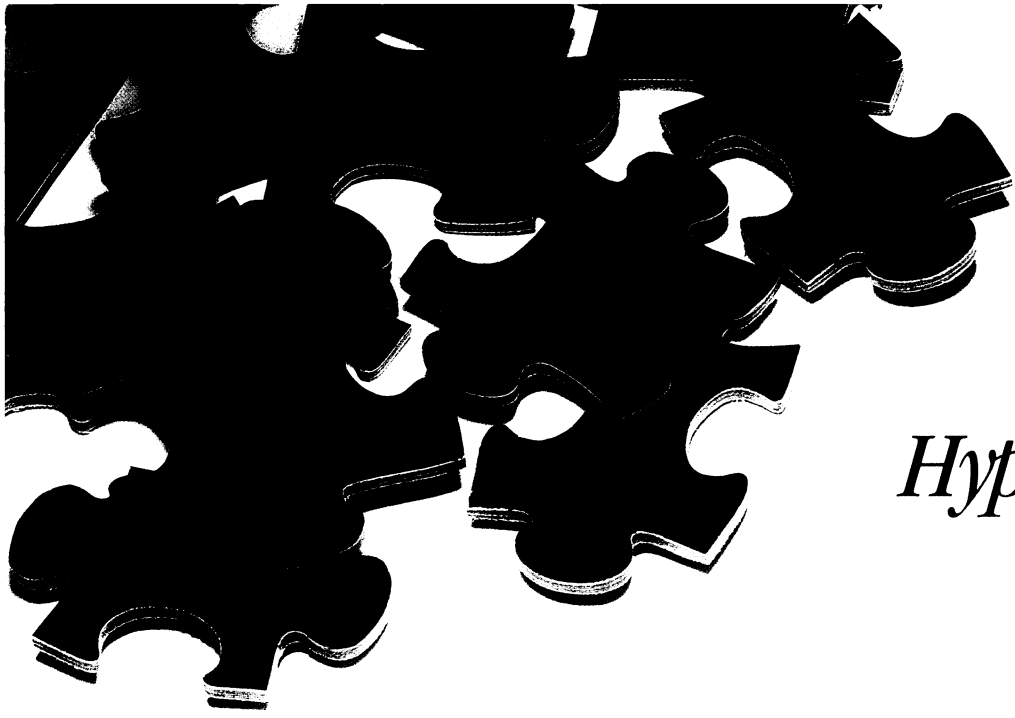
For prescribing information see page 1327

Boehringer Ingelheim

Dedicated to Respiratory Care

**Atrovent®** (ipratropium bromide)
INHALER
**The Anticholinergic Advantage**

PAAB



*In the puzzle of Hypertension Control...*

# When an ACE inhibitor alone no longer fits the need

# ℙ VASERETIC® can meet the challenge

(enalapril maleate-hydrochlorothiazide tablets)

## Convenience

- Once-a-day with or without food

## Control

- Enalapril and HCTZ – a clinically proven combination[1]

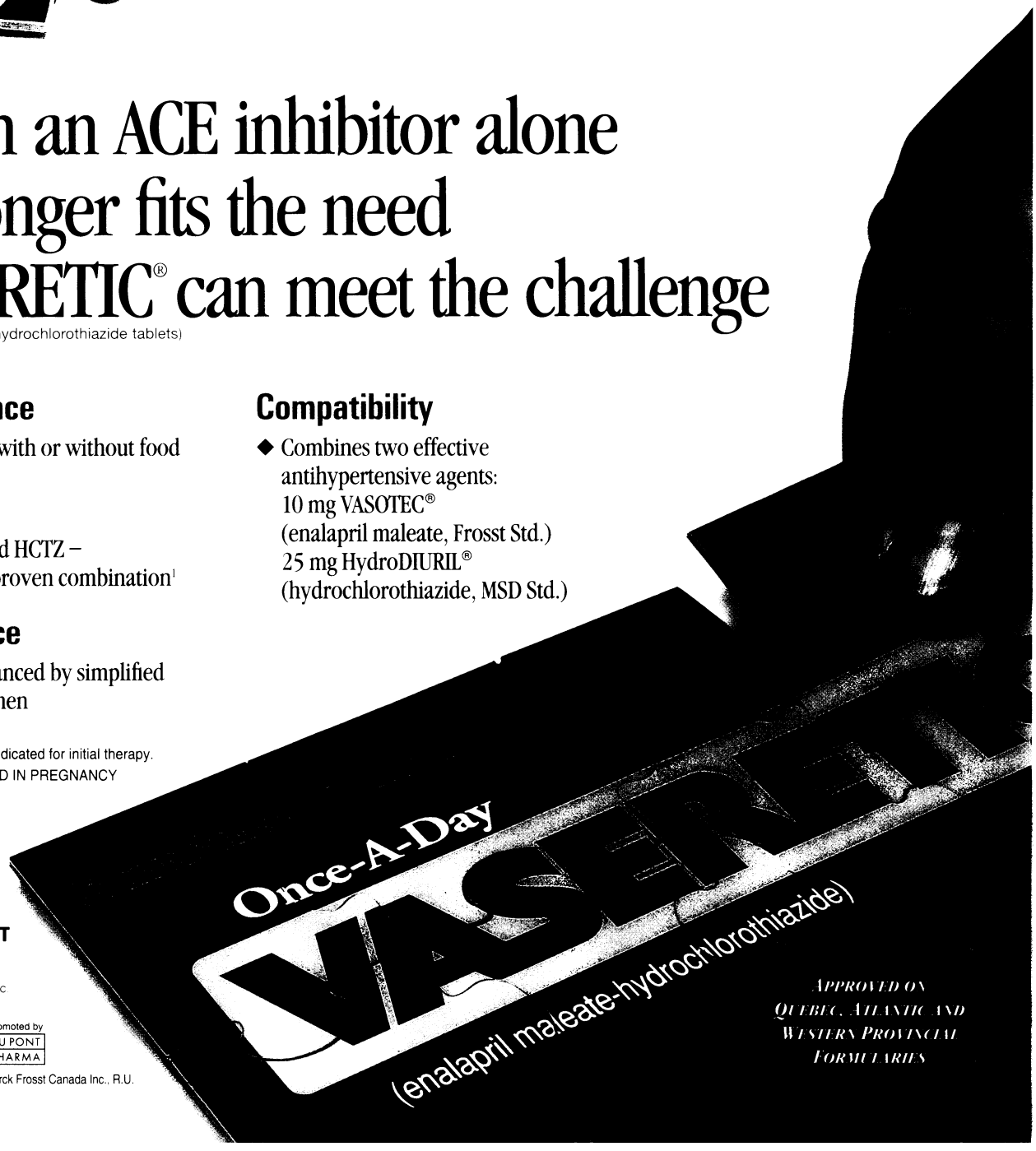
## Compliance

- May be enhanced by simplified dosing regimen

## Compatibility

- Combines two effective antihypertensive agents:
  10 mg VASOTEC®
  (enalapril maleate, Frosst Std.)
  25 mg HydroDIURIL®
  (hydrochlorothiazide, MSD Std.)

VASERETIC® is not indicated for initial therapy.
NOT RECOMMENDED IN PREGNANCY




*Approved on Quebec, Atlantic and Western Provincial Formularies*

MERCK FROSST

FROSST
DIV. OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC

MEMBER PMAC PAAB

Promoted by DU PONT PHARMA

CRN-92-CDN-5931-JA

# For acute exacerbations of chronic bronchitis

# Cipro can eradicate the infection and reduce the cycle of lung damage

▼ Patients with chronic bronchitis have impaired lung function and reduced host defence mechanisms. Acute bacterial infections and the resulting inflammation can lead to further lung damage.[1] Prompt microbial eradication is essential to reduce the direct and indirect damage caused by the organisms to the lungs.[1,2]

▼ Cipro offers dependable clinical efficacy for the treatment of acute bronchitis in patients with underlying chronic lung inflammation.[3,4] Its broad spectrum coverage of the most commonly isolated respiratory tract pathogens includes both gram negative and gram positive organisms.[5] And Cipro has excellent penetration into the bronchial mucosa, resulting in concentrations at the site of infection that are well above those necessary to eradicate the microorganisms.[6]

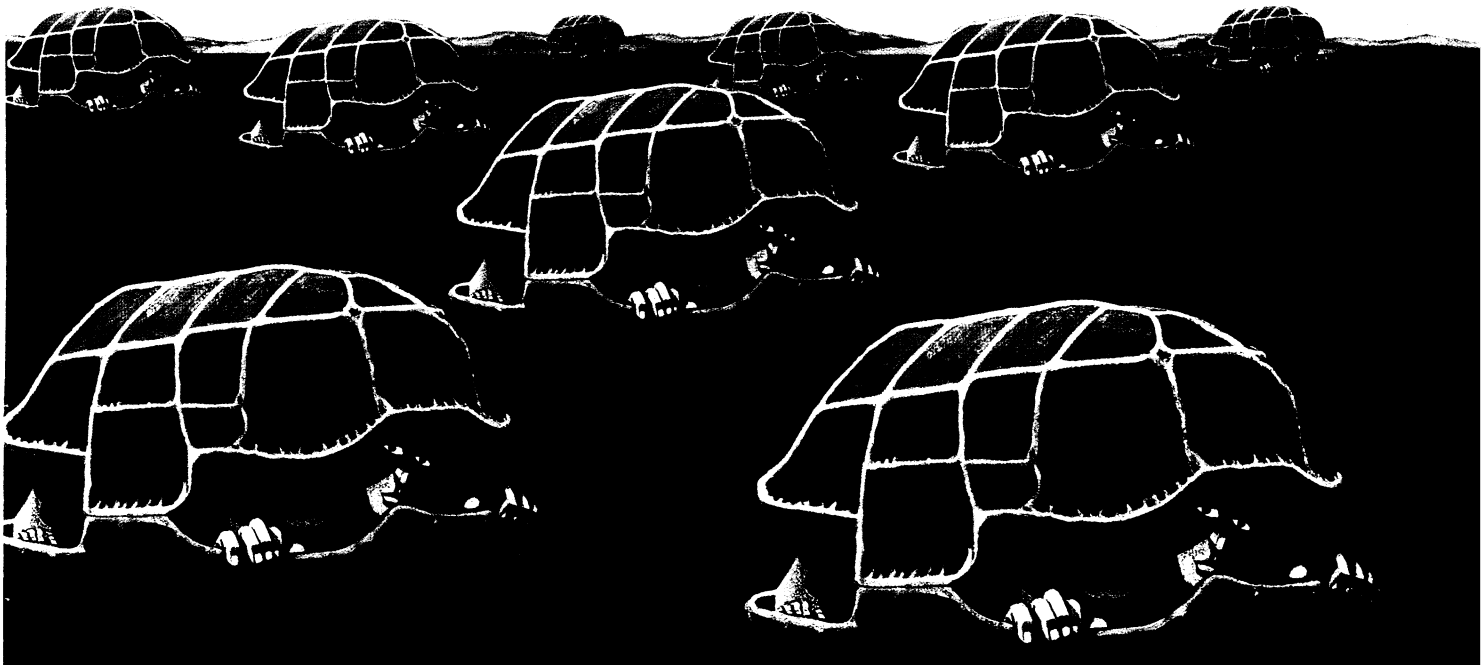
▼ For the treatment of acute exacerbations of chronic bronchitis, depend on Cipro. Proven efficacy in a convenient B.I.D. dose.

Cipro may be indicated for the following; *E. cloacae, E. coli, H. influenzae, K. pneumoniae, P. mirabilis, P. aeruginosa, S. aureus, S. pneumoniae.* Most frequently observed side effects are; nausea (1.3%), diarrhea (1%).

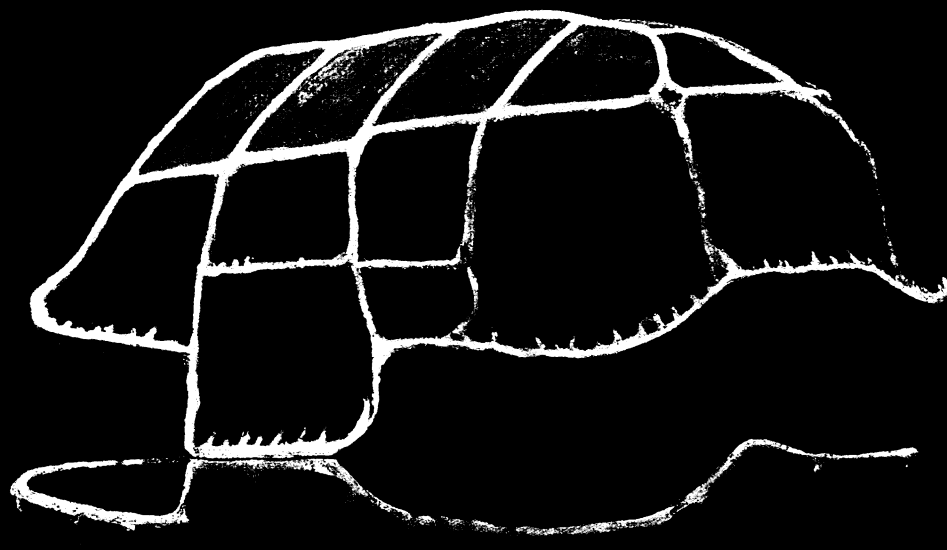
Dome PAAB

Cipro® Depend on it

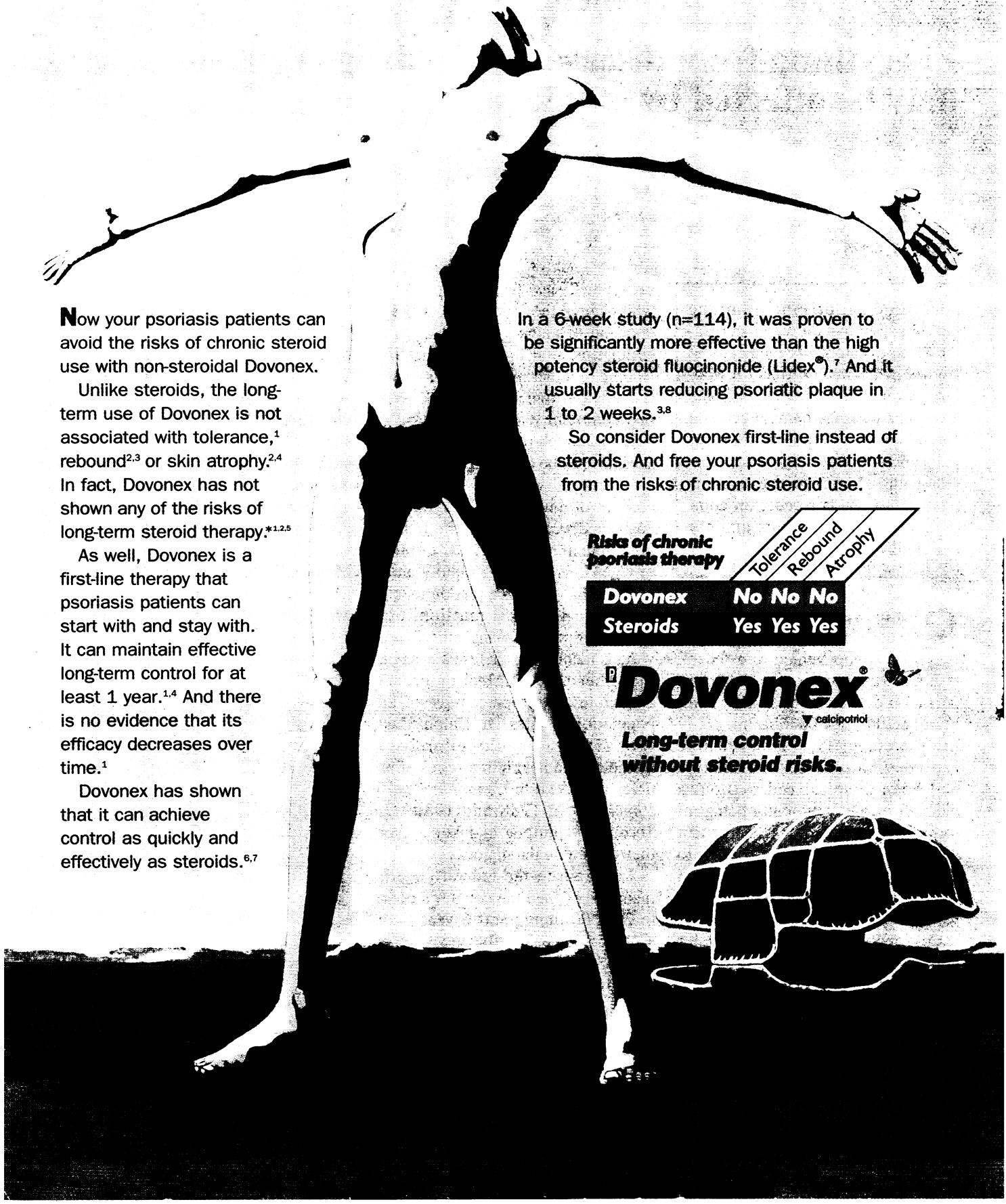
*ciprofloxacin hydrochloride*



# Now you can free psoriasis patients from the risks of chronic steroid use.



# Choose non-steroidal Dovonex. For long-term control of psoriasis without steroid risks.



Now your psoriasis patients can avoid the risks of chronic steroid use with non-steroidal Dovonex.

Unlike steroids, the long-term use of Dovonex is not associated with tolerance,[1] rebound[2,3] or skin atrophy.[2,4] In fact, Dovonex has not shown any of the risks of long-term steroid therapy.*[1,2,5]

As well, Dovonex is a first-line therapy that psoriasis patients can start with and stay with. It can maintain effective long-term control for at least 1 year.[1,4] And there is no evidence that its efficacy decreases over time.[1]

Dovonex has shown that it can achieve control as quickly and effectively as steroids.[6,7]

In a 6-week study (n=114), it was proven to be significantly more effective than the high potency steroid fluocinonide (Lidex®).[7] And it usually starts reducing psoriatic plaque in 1 to 2 weeks.[3,8]

So consider Dovonex first-line instead of steroids. And free your psoriasis patients from the risks of chronic steroid use.

| *Risks of chronic psoriasis therapy* | Tolerance | Rebound | Atrophy |
|---|---|---|---|
| Dovonex | No | No | No |
| Steroids | Yes | Yes | Yes |

**Dovonex®**
▼ calcipotriol

***Long-term control without steroid risks.***

# CANADA'S INTERNATIONAL IMMUNIZATION PROGRAM

# HELPING CHILDREN BEAT THE ODDS

Canada is an important partner in the global effort to help children in the developing world beat the odds against six deadly, but preventable, diseases. Today, 80 per cent of children under the age of one are protected against *measles, polio, tuberculosis, tetanus, whooping cough* and *diphtheria* – compared to only five per cent 20 years ago.

That translates into more than three million young lives saved each year. Despite these encouraging statistics, nearly two million children a year still die for lack of immunization. The odds can be beaten with your help.

For more information on how you can help support this program, please contact:

**Canadian Public Health Association**

1565 Carling Avenue
Suite 400
Ottawa, Ontario
Canada K1Z 8R1
Telephone: (613) 725-3769
Fax: (613) 725-9826

**YES,** I want to help support this program. Please send me the "Helping Children Beat the Odds" information package.

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Send this coupon by fax or mail today. Thank you for your interest and support.

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Canada's International Immunization Program is financially supported by CIDA.

# With depression, even a favourite pastime can seem overwhelming.

## Luvox* helps put the joy back into life.

Luvox* fluvoxamine is a highly selective serotonin reuptake inhibitor.[1,2] So it can offer patients efficacy comparable to the tricyclic antidepressants.[2-7] Yet its safety and side effect profiles† are clearly different.[1-7]

That can mean fewer anticholinergic and cardiovascular effects.‡[2-8] As well as reduced risk if overdose occurs.[2,3,9]

In addition, Luvox* has a short half-life and few drug interactions, so it may be particularly useful in patients with a slower metabolism.[1-3]

Help your depressed patients rediscover the joy in life. Prescribe Luvox.* Now covered on all provincial drug plans.

**Luvox**
fluvoxamine maleate

CAN HELP WITH LESS HURT

McNEIL PHARMACEUTICAL

PAAB CCPP MEMBER PMAC

SOLVAY KINGSWOOD

†As with other SSRI's, the most common side effects observed with Luvox* relate to the digestive system.[2] Side effects are usually transient and infrequently lead to discontinuation. ‡Patients with a recent history of myocardial infarction or unstable heart disease were excluded from pre-marketing studies.

For prescribing information see page 1332

# INHIBACE™: POTENT ACE INHIBITION FOR SUPPRESSING ANGIOTENSIN II IN THE VASCULATURE[1,2]

## AN ACE INHIBITOR CREATED BY 3-D COMPUTER MODELLING

'Inhibace' was conceived by three-dimensional computer modelling techniques to be highly specific and selective at the active site of angiotensinogen.[1]

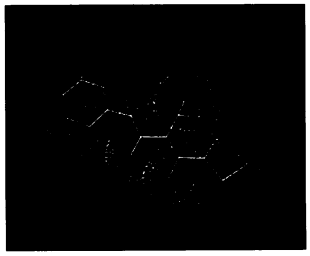


*Figure 4: Close Up On Three Dimensional Modelling*

## EFFECT ON ACE INHIBITION

Following administration of new 'Inhibace', plasma ACE activity is inhibited more than 90% within two hours of therapeutic doses.[1,2]

## EFFECT ON VASCULATURE

In ex vivo studies, oral administration of new 'Inhibace' significantly inhibited plasma ACE activity (up to 96%) and tissue ACE activity in a number of arteries and veins.[1,2]

## EFFECT ON VASCULAR STRUCTURE

Animal studies suggest that treatment with 'Inhibace' can reduce vascular smooth muscle cell growth in a number of vessels of hypertensive rats.[3] Further studies have shown that 'Inhibace' can prevent an increase in the media/lumen ratio of resistance arteries.[4]

Human studies are currently being conducted to support these findings.

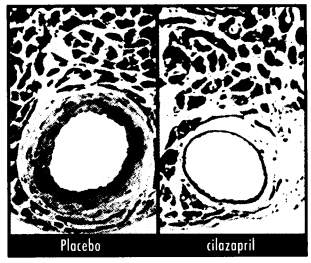



*Figure 5: Cross Section of Coronary Arteries of Spontaneously Hypertensive Rats*[3]

## EFFECT ON RENAL FUNCTION

Renal blood flow, GFR and renal function may be improved or preserved.[1,5]

Dosage: Start with 2.5 mg once-a-day

## BENEFITS OF INHIBACE™

- Effective blood pressure control with once daily dosing, confirmed by 24 hour ambulatory blood pressure monitoring[1,6]
- Functional changes in the kidney due to target organ damage may improve[1,3,5]
- Very low incidence of lifestyle-limiting side effects, especially cough, fatigue and dizziness[1]
- Few contraindications[1]
- For a broad range of hypertensive patients†

*†Suitable when diuretics and beta-blockers are inappropriate*
*† 'Inhibace' should not be used in pregnancy*

PAAB
Hoffmann-La Roche Limited
Mississauga, Ontario L5N 6L7

Roche®

NEW ONCE-A-DAY

cilazapril

℞ INHIBACE™

Fight the Effects of Angiotensin II & Hypertension

For prescribing information see page 1346

APRIL 15, 1994

# VASOSELECTIVE RENEDIL®

# ONCE-A-DAY

felodipine

2.5 mg / 5 mg / 10 mg

Extended Release Tablets

**RENEDIL®** (felodipine) **Extended Release Tablets** (2.5 mg, 5 mg and 10 mg)

**THERAPEUTIC CLASSIFICATION** Antihypertensive Agent. **ACTION AND CLINICAL PHARMACOLOGY** RENEDIL (felodipine) is a calcium ion influx inhibitor (calcium channel-blocker). Felodipine is a member of the dihydropyridine class of calcium channel-blockers. **Mechanism of Action** The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into cardiac muscle and vascular smooth muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium into the cells through specific ion channels. Felodipine blocks transmembrane influx of calcium through the slow channel without affecting to any significant degree the transmembrane influx of sodium through the fast channel. This results in a reduction of free calcium ions available within cells of the above tissues. Felodipine does not alter total serum calcium. In vitro studies show that the effects of felodipine on contractile mechanisms are selective, with greater effects on vascular smooth muscle than on cardiac muscle. Negative inotropic effects have been detected in vitro, but such effects have not been seen in intact animals. The effect of felodipine on blood pressure in man is principally a consequence of a dose-related decrease in peripheral vascular resistance, with a modest reflex increase in heart rate (see Pharmacodynamics). **PHARMACOKINETICS** Felodipine is completely absorbed from the gastrointestinal tract after oral administration. Due to rapid biotransformation of felodipine during its first pass through the portal circulation, the systemic availability is approximately 20% and is independent of the dose in the range of 5-20 mg per day. The plasma protein binding of felodipine is approximately 99%. It is bound predominately to the albumin fraction. Felodipine is extensively metabolized by the liver. After 72 hours, approximately 70% of a given oral dose is excreted as metabolites in the urine and 10% is excreted in the faeces. Less than 0.5% of an oral dose is recovered unchanged in the urine. Six metabolites, which account for 23% of the oral dose, have been identified: none has significant vasodilating activity. Following oral administration of the immediate-release formulation, the plasma level of felodipine declines polyexponentially with mean terminal $t_{1/2}$ of 11 to 16 hours, in young healthy volunteers. The extended release formulation prolongs the absorption phase of felodipine resulting in an increased time to reach peak plasma concentrations ($t_{max}$), and a reduced maximum plasma concentration ($C_{max}$). The mean $t_{max}$ ranges from 2.5 to 5 hours. The area under the plasma concentration versus time curve and $C_{max}$ are linearly related to the dose in the 10 to 40 mg range. Following administration of RENEDIL to hypertensive patients, mean $C_{max}$ at steady state is approximately 20% higher after multiple doses than after a single dose. No increase in the AUC is found during multiple dosing. The inter- individual variation in $C_{max}$ and AUC after repeated dosing is approximately threefold and indicates a need for individualized dosing. The bioavailability of felodipine is not influenced by the presence of food in the gastrointestinal tract. In a study of six patients, the bioavailability of felodipine when taken as plain tablets, was increased more than twice when taken with concentrated grapefruit juice, compared to when taken with water or orange juice. A similar finding has been seen with some other dihydropyridine calcium antagonists but to a lesser extent than that seen with felodipine. Plasma concentrations of felodipine, after a single oral dose and at steady state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74 years) was only 45 percent of that in young volunteers (mean age 26 years). At steady state mean AUC for young patients was 39 percent of that for the elderly patients. In patients with hepatic disease, the clearance of felodipine was reduced to about 60 percent of that seen in normal young volunteers. Renal impairment does not alter the plasma concentration profile of felodipine. Although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are haemodynamically inactive. Animal studies have demonstrated that felodipine crosses the blood-brain barrier and the placenta. **PHARMACODYNAMICS Hemodynamic Effects** The acute hemodynamic effect of felodipine is a reduction in total peripheral resistance which leads to a decrease in blood pressure associated with a modest reflex increase in heart rate. This reflex increase in heart rate frequently occurs during the first week of therapy and generally attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic administration. The effect on the heart rate is inhibited by beta-blocking agents. Following administration of RENEDIL a reduction in blood pressure generally occurs within two to five hours. During chronic administration, substantial blood pressure control lasts for approximately 24 hours; reductions in diastolic blood pressure at trough plasma levels were 40-50 percent of those at peak plasma levels. The antihypertensive effect is dose-dependent and correlates with the plasma concentration of felodipine. **Electrophysiological Effects** Felodipine in therapeutic doses has no effect on conduction in the conducting system of the heart and no effect on A-V nodal refractoriness. No direct additional effects to those registered after beta-blockade are observed when RENEDIL is given concomitantly. **Renal Effects** Renal vascular resistance is decreased by felodipine while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis, and kaliuresis have been observed during the first week of therapy. No significant effects on serum electrolytes were observed during short and long-term therapy. No general salt and water retention occurs during long-term therapy. In clinical trials increases in noradrenaline plasma levels have been observed. **INDICATIONS AND CLINICAL USE** RENEDIL (felodipine) is indicated in the treatment of mild to moderate essential hypertension. RENEDIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. RENEDIL can be tried as initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of RENEDIL with a thiazide diuretic or a beta-blocker has been found to be compatible and showed an additive antihypertensive effect. Safety and efficacy of concurrent use of RENEDIL with other antihypertensive agents has not been established. **CONTRAINDICATIONS** RENEDIL (felodipine) is contraindicated in: 1) Patients with a known hypersensitivity to felodipine or other compounds of the dihydropyridine class. 2) Women of childbearing potential, in pregnancy, and during lactation. Fetal malformations and adverse effects on pregnancy have been reported in animals. **Teratogenic Effects** Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3, and 4.6 mg/kg/day (from 0.4 to 4 times the maximum recommended human dose on a mg/m$^2$ basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class. Similar fetal anomalies were not observed in rats given felodipine. In a teratology study in cynomolgus monkeys, no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses. **Non-teratogenic Effects** In a study on fertility and general reproductive performance in rats, prolongation of parturition with difficult labour and an increased frequency of fetal and early postnatal deaths were observed in the groups treated with doses of 9.6 mg/kg/day and above. Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day. This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys. **WARNINGS Congestive Heart Failure** The safety and efficacy of RENEDIL (felodipine) in patients with heart failure have not been established. Caution should, therefore, be exercised when using RENEDIL in hypertensive patients with compromised ventricular function, particularly in combination with a beta-blocker. Acute hemodynamic studies in a small number of patients with New York Heart Association Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects. **Hypotension, Myocardial Ischemia** RENEDIL may occasionally, precipitate symptomatic hypotension and rarely syncope. It may lead to reflex tachycardia which, particularly in patients with severe obstructive coronary artery disease, may result in myocardial ischaemia. Careful monitoring of blood pressure during the initial administration and titration of felodipine is recommended. Care should be taken to avoid hypotension especially in patients with a history of cerebrovascular insufficiency, and in those taking medications known to lower blood pressure. **Beta-Blocker Withdrawal** RENEDIL gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blockers. **Outflow obstruction** RENEDIL should be used with caution in the presence of fixed left ventricular outflow obstruction. **PRECAUTIONS Peripheral edema** Mild to moderate peripheral edema was the most common adverse event in the clinical trials. The incidence of peripheral edema was dose-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction. **Use in Elderly Patients or in Patients with Impaired Liver Function** Patients over 65 years of age as well as patients with impaired liver function may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of RENEDIL. These patients should have their blood pressure monitored closely during the initial administration and dosage adjustment of RENEDIL, and should rarely require doses above 10 mg per day. (See Pharmacokinetics and DOSAGE AND ADMINISTRATION). **Gingival Hyperplasia** RENEDIL can induce gingival enlargement in patients with pronounced gingivitis and parodontitis. However, such changes may be reversed by measures of good oral hygiene and mechanical debridement of the teeth. **Pregnancy and Lactation** See CONTRAINDICATIONS **Use in Children** RENEDIL is not recommended in children since the safety and efficacy in children have not been established. **Drug Interactions** Beta-Adrenoceptor Blocking Agents: A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and $C_{max}$ of metoprolol, however, were increased approximately 31 and 36 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated. Cimetidine: In healthy volunteers pharmacokinetic studies showed an approximately 50 percent increase in the area under the felopidine plasma concentration time curve (AUC) as well as the $C_{max}$ of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of RENEDIL be used when given concomitantly with cimetidine. Digoxin: When given concomitantly with felodipine as conventional tablets the peak plasma concentration of digoxin was significantly increased. With the extended release formulation of felodipine there was no significant change in peak plasma levels or AUC of digoxin. Phenytoin, carbamazepine and phenobarbital: In a pharmacokinetic study maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long term anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in healthy volunteers. The mean area under the felodipine plasma concentration-time curve was also reduced in epileptic patients to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

**RECOMMENDED STARTING DOSE: RENEDIL 5 mg once-a-day**

***Rx in 28's***

**Other Concomitant Therapy:** In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone. **ADVERSE REACTIONS** In 1102 patients treated with felodipine, either alone or in combination with other antihypertensive agents, adverse events were reported in 52% of patients and caused discontinuation of therapy in 9%. The most common adverse events (incidence of at least 1%) were: peripheral edema (21.3%), headache (14.9%), feeling of warmth/flush (13.2%), dizziness/vertigo (4.6%), fatigue (2.4%), palpitation (1.6%), extrasystoles (1.5%), nausea (1.5%), pain (1.5%), paraesthesia (1.2%), chest pain (1.1%). In addition, the following events were reported with an incidence of less than 1 percent **(Adverse Events that were Judged Serious are in Bold Face):** Cardiovascular: **angina pectoris, myocardial infarction, atrial fibrillation,** arrhythmia, abnormal ECG, AV block, bundle branch block, postural hypotension, syncope, tachycardia, bradycardia. Central & Peripheral Nervous System: **brain stem disorder,** tremor, abnormal gait, anxiety, depression, insomnia, nervousness, somnolence, agitation, apathy, increased appetite, impaired concentration, confusion, emotional lability, hallucination, sleep disorder, malaise. Gastrointestinal: **abnormal hepatic function,** cholestatic hepatitis, abdominal pain, vomiting, constipation, diarrhoea, dyspepsia, dysphagia, flatulence, gingivitis, gum hyperplasia, gingival bleeding, dry mouth, salivary gland enlargement. Dermatologic: photosensitivity reaction, erythema nodosum, eczema, pruritus, rash, increased sweating. Musculo-skeletal: arthralgia, myalgia. Respiratory: cough, dyspnoea. Genito-urinary: impotence, dysuria, frequent urination. Others: abnormal vision, anemia, substernal chest pain, asthenia, generalized edema, periorbital edema, facial edema, change in weight, chills. Laboratory tests: For the following laboratory values statistically significant decreases were observed; bilirubin, red blood cell count, hemoglobin, and urate. Statistically significant increases were found in erythrocyte sedimentation rate and thrombocyte count. None of these changes were considered to be of clinical significance. In addition, the following abnormal blood chemistry results were reported: hypokalemia, hyperkalemia, hyponatremia. **SYMPTOMS AND TREATMENT OF OVERDOSAGE Symptoms** Overdosage can cause excessive peripheral vasodilatation with marked hypotension and possible bradycardia. **Treatment** If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The intravenous administration of fluids may be used to treat hypotension. Plasma volume may be increased by infusion of a plasma volume expander. When accompanied by bradycardia, atropine 0.5-1 mg should be administered intravenously. Sympathomimetic drugs predominantly affecting the $\alpha_1$-adrenoceptor may be given if the above-mentioned measures are considered insufficient. Removal of felodipine from the circulation by hemodialysis has not been established. **DOSAGE AND ADMINISTRATION** RENEDIL (felodipine) should be swallowed whole and not crushed or chewed. The dose should be adjusted individually according to patient response. The recommended initial dose is 5 mg once daily. The 2.5 mg tablet is available for dose titration purposes. The usual maintenance dosage range is 5-10 mg once daily. Dose adjustment, if necessary, should be done at intervals of not less than two weeks. The maximum recommended daily dose is 20 mg once a day. In clinical trials, 20 mg once daily showed an increased blood pressure response but also a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment. **Use in the Elderly or in Patients with Impaired Liver Function** Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine (see PRECAUTIONS). In these patients, an initial treatment of 2.5 mg daily should be considered. In general, doses above 10 mg should not be considered in these patients. **AVAILABILITY** RENEDIL (felodipine) are extended release, film-coated tablets, containing felodipine in strengths of 2.5 mg, 5 mg and 10 mg. RENEDIL 2.5 mg Tablet: A yellow, circular, biconvex, film-coated tablet, engraved H/FF on one side. RENEDIL 5 mg Tablet: A pink, circular, biconvex film-coated tablet, engraved H/FC on one side. RENEDIL 10 mg Tablet: A red-brown, circular, biconvex film-coated tablet, engraved H/FD on one side. Each tablet strength is available in HDPE bottles (100 tablets) and compliance blister packages (28 tablets). NOTE: These extended release tablets must not be divided, crushed or chewed.

Product Monograph available upon request.

References: 1. Gradman AH: Hemodynamic effects of the vascular selective calcium antagonist felodipine in patients with impaired left ventricular function. *Am Heart J*, 1992;123(1):273-278.
2. Product Monograph. 3. Fariello R et al: Extended release felodipine in essential hypertension. *AJH*, 1991;4:27-33.
4. Data on file, Hoechst-Roussel Canada Inc., July 1993.

**Hoechst-Roussel Canada Inc.**

Montréal, Québec

PAAB ADREN 05/94

once daily

# Nasacort* Nasal Inhaler

(triamcinolone acetonide)

## THERAPEUTIC CLASSIFICATION

Corticosteroid for nasal use

**ACTIONS AND CLINICAL PHARMACOLOGY:** Triamcinolone acetonide is a potent anti-inflammatory steroid with strong topical and weak systemic activity. When administered intranasally in therapeutic doses, it has a direct anti-inflammatory action on the nasal mucosa, the mechanism of which is not yet completely defined. The minute amount absorbed in therapeutic doses has not been shown to exert any apparent clinical systemic effects.

**INDICATIONS AND CLINICAL USE:** NASACORT* (triamcinolone acetonide) nasal inhaler is indicated for the topical treatment of the symptoms of perennial and seasonal allergic rhinitis unresponsive to conventional treatment.

**CONTRAINDICATIONS:** Active or quiescent tuberculosis or untreated fungal, bacterial and viral infection. Hypersensitivity to any of the ingredients of NASACORT* (triamcinolone acetonide).

**WARNINGS:** In patients previously on prolonged periods or high doses of systemic steroids, the replacement with a topical corticosteroid can be accompanied by symptoms of withdrawal, e.g. joint and/or muscular pain, lassitude, and depression; in severe cases, adrenal insufficiency may occur, necessitating the temporary resumption of systemic steroid therapy. Careful attention must be given to patients with asthma or other clinical conditions in whom a rapid decrease in systemic steroids may cause a severe exacerbation of their symptoms.
**Pregnancy:** See Precautions.

**PRECAUTIONS:**

1) The replacement of a systemic steroid with NASACORT* (triamcinolone acetonide) has to be gradual and carefully supervised by the physician. The guidelines under "Administration" should be followed in all such cases.

2) During long-term therapy pituitary-adrenal function and hematological status should be assessed.

3) Patients should be informed that the full effect of NASACORT* therapy is not achieved until 2 to 3 days of treatment have been completed. Treatment of seasonal rhinitis should, if possible, start before the exposure to allergens.

4) Treatment with NASACORT* should not be stopped abruptly but tapered off gradually.

5) Corticosteroids may mask some signs of infection and new infections may appear. A decreased resistance to localized infections has been observed during corticosteroid therapy; this may require treatment with appropriate therapy or stopping the administration of NASACORT*.

6) The long-term effects of NASACORT* are still unknown, in particular, its local effects; the possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

7) There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypothrombinemia.

8) Because of the inhibitory effect of corticosteroids on wound healing, in patients who have had recent nasal surgery or trauma, a nasal corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

9) Patients should be advised to inform subsequent physicians of prior use of corticosteroids.

10) Until greater clinical experience has been gained, the continuous, long-term treatment of children under age 12 is not recommended.

11) **Pregnancy:** The safety of NASACORT* in pregnancy has not been established. If used, the expected benefits should be weighed against the potential hazard to the fetus, particularly during the first trimester of pregnancy.

    Like other glucocorticosteroids, triamcinolone acetonide is teratogenic to rodents and non-human primates (see under TOXICOLOGY). The relevance of these findings to humans has not yet been established. Infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy should be carefully observed for hypoadrenalism.

12) **Lactation:** Glucocorticosteroids are secreted in human milk. It is not known whether triamcinolone acetonide would be secreted in human milk, but it is suspected to be likely. The use of NASACORT* in nursing mothers, requires that the possible benefits of the drug be weighed against the potential hazards to the infant.

13) **Children:** NASACORT* is not presently recommended for children younger than 12 years of age due to limited clinical data in this age group.

14) Fluorocarbon propellants may be hazardous if they are deliberately abused. Inhalation of high concentrations of aerosol sprays has brought about cardiovascular toxic effects and even death, especially under conditions of hypoxia. Aerosols are safe when used properly and with adequate ventilation, but excessive use should be avoided.

15) To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of NASACORT* (see Patient Instructions).

**ADVERSE REACTIONS:** Adverse reactions reported in both controlled and uncontrolled studies involving 1148 patients who received NASACORT* (triamcinolone acetonide) are provided in the following table:

| Adverse Experience | NASACORT % (n=1077) | Placebo % (n=545) |
|---|---|---|
| Headache | 20.4 | 19.4 |
| Upper Respiratory Infection | 5.3 | 8.1 |
| Nasal Irritation | 5.1 | 4.2 |
| Throat Discomfort | 4.6 | 3.3 |
| Dry Mucous Membranes | 3.5 | 2.2 |
| Epistaxis | 4.6 | 6.6 |
| Sneezing | 3.1 | 5.5 |
| Sinusitis | 2.1 | 3.7 |

When patients are transferred to NASACORT* from a systemic steroid, allergic conditions such as asthma or exzema may be unmasked (see Warnings).

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** Like any other nasally administered corticosteroid, acute overdosing is unlikely in view of the total amount of active ingredient present. However when used chronically in excessive doses or in conjunction with other corticosteroid formulations, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes recur, the dosage of NASACORT* (triamcinolone acetonide) should be discontinued slowly consistent with accepted procedures for discontinuation of chronic steroid therapy. (see Administration). The restoration of hypothalamic-pituitary axis may be slow; during periods of pronounced physical stress (i.e. severe infections, trauma, surgery) a supplement with systemic steroids may be advisable.

**DOSAGE AND ADMINISTRATION:** See Warnings.
NASACORT* (triamcinolone acetonide) is not recommended for children under 12 years of age.

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to NASACORT*. Initially, NASACORT* and the systemic corticosteroid must be given concomitantly, while the dose of the latter is gradually decreased. The usual rate of withdrawal of the systemic steroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 2.5 mg of prednisone (or equivalent) every ten days. If withdrawal symptoms appear, the previous dose of the systemic steroid should be resumed for a week before further decrease is attempted.

The therapeutic effects of corticosteroids, unlike those of decongestants, are not immediate. Since the effect of NASACORT* depends on its regular use, patients must be instructed to take the nasal inhalations at regular intervals and not as with other nasal sprays, as they feel necessary.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases it is advisable to use a nasal vasoconstrictor for two to three days prior to NASACORT* therapy. Patients should be instructed on the correct method of use, which is to blow the nose, then insert the nozzle firmly into the nostril, compress the opposite nostril and actuate the spray while inspiring through the nose, with the mouth closed.

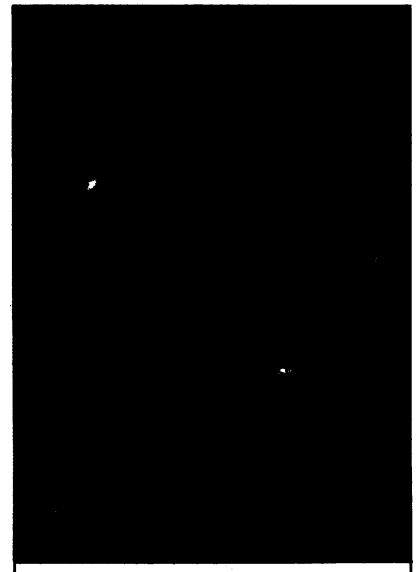
An improvement of symptoms usually becomes apparent within a few days after the start of therapy. However, symptomatic relief may not occur in some patients for as long as two weeks. NASACORT* should not be continued beyond three weeks in the absence of significant symptomatic improvement.

**Adults and Children 12 years of age and older:** The recommended starting dose of NASACORT* is 400 µg per day given as two sprays (100 µg/spray) in each nostril once a day. If needed, the dose may be increased to 800 µg per day (100 µg/spray) either as once a day dosage or divided up to four times a day, i.e., twice a day (two sprays/nostril), or four times a day (one spray/nostril).

After the desired effect is obtained, patients may be maintained on a dose of one spray (100 µg) in each nostril once a day (total daily dose: 200 µg per day).

**AVAILABILITY:** NASACORT* (triamcinolone acetonide) is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in the propellant dichlorodifluoromethane and dehydrated alcohol USP 0.7% w/w. Each canister contains 15 mg triamcinolone acetonide. Each actuation releases approximately 100 µg triamcinolone acetonide of which approximately 55 µg are delivered from the nasal actuator to the patient (estimated from *in vitro* testing). There are at least 100 actuations in one NASACORT* canister. The device should not be used after 100 inhalations, since the amount delivered thereafter per actuation may not be consistent. It is supplied with a nasal adapter and patient instructions: Box of one.

References: 1. Day JH et al. Early onset of action of triamcinolone acetonide nasal spray as determined by a controlled antigen delivery in ragweed allergic subjects. Abstract presented at The American Academy of Allergy and Immunology, March 5, 1994. Data on file, Rhône-Poulenc Rorer Canada Inc., 1994. 2. NASACORT product monograph, Rhône-Poulenc Rorer Canada Inc.



**Brings Rhinitis Symptoms Promptly Down To Size**

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# Pr VASERETIC®

(enalapril maleate and hydrochlorothiazide tablets)

Tablets 10 mg/25 mg

**Angiotensin Converting Enzyme Inhibitor/Diuretic**

## INDICATIONS AND CLINICAL USE

The treatment of essential hypertension when this combination therapy is appropriate. Consider the risk of angioedema (see WARNINGS). Used when diuretics or *beta*-blocker are ineffective or associated with unacceptable adverse effects.

Not indicated as initial therapy. Patients can develop symptomatic hypotension when enalapril and diuretic are initiated simultaneously (see Drug Interactions). Titrate patients on individual drugs. If combination represents the dose and frequency determined during titration, VASERETIC® may be more convenient for patients.

**Use of ACE inhibitors during the second and third trimesters of pregnancy can cause injury or death of a developing fetus. When pregnancy is detected, discontinue VASERETIC® as soon as possible (see WARNINGS; Use in Pregnancy).**

## CONTRAINDICATIONS

Hypersensitivity to any component of this product or to other sulfonamide-derived drugs; history of angioneurotic edema related to ACE inhibitor therapy; and patients with anuria.

## WARNINGS

**Angioedema** has been reported. Angioedema associated with laryngeal edema and/or shock may be fatal. In such cases, discontinue drug promptly and observe patient until swelling subsides. Swelling confined to the face, lips, and mouth usually resolves without treatment, although antihistamines may be useful in relieving symptoms. However, where there is involvement of the tongue, glottis and larynx, likely to cause airway obstruction, prompt administration of subcutaneous adrenaline (0.5mL 1:1000) may be indicated. Patients with a history of angioedema, unrelated to ACE inhibitor use, may be at increased risk (see CONTRAINDICATIONS).

**Symptomatic hypotension** has occurred, usually during initial therapy or when the dose was increased, and is more likely in patients who are volume-depleted. VASERETIC® should not be used to start therapy or when a dose change is needed. In patients with severe congestive heart failure, excessive hypotension may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. For patients in whom the excessive hypotension could result in severe or fatal complications, i.e. those with ischemic heart or cerebrovascular disease - start therapy with enalapril maleate under close medical supervision, usually in a hospital. Such patients should be followed closely for the potential fall in blood pressure during first two weeks of therapy or when enalapril and/or hydrochlorothiazide is increased. If hypotension occurs, place patient in supine position and if needed, administer IV infusion of normal saline. A transient hypotensive response is not a contraindication to further doses.

**Neutropenia/agranulocytosis** and bone marrow depression have been caused by ACE inhibitors. Current experience with enalapril shows incidence to be rare. Consider periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease.

**Azotemia** may be caused or increased by hydrochlorothiazide. Cumulative effects may occur in renally-impaired patients. Discontinue the diuretic if increasing azotemia or oliguria occur in patients with severe progressive renal disease.

**Impaired Renal Function:** Renal function should be assessed before initiating therapy with enalapril. Patients with renal insufficiency may require reduced or less frequent doses. Thiazides may not be appropriate and are ineffective at creatinine clearance ≤ 30 mL/min. Some hypertensive patients with no apparent renal disease have developed increases in BUN and creatinine while on concurrent diuretic/enalapril therapy. Discontinue VASERETIC® if this occurs.

Renal failure, which has been reported mainly in patients with underlying renal disease including renal artery stenosis, is usually reversible when treated promptly. Close monitoring during therapy should be performed as deemed appropriate in patients with renal insufficiency.

**Impaired liver function:** Hepatitis, jaundice (hepatocellular and/or cholestatic),elevation of liver enzymes and/or serum bilirubin, which have occurred in patients with or without pre-existing liver abnormalities, were usually reversed on discontinuation of enalapril. For any unexplained symptoms, particularly within the first months of treatment, a full set of liver function tests and other necessary investigations are recommended. Consider discontinuation of enalapril when appropriate. Use enalapril with particular caution in patients with pre-existing liver abnormalities. Obtain baseline liver function tests before initiating therapy and monitor response and metabolic effects closely. Use thiazides with caution in patients with impaired hepatic function or progressive liver disease since minor changes of fluid and electrolyte balance may cause hepatic coma.

**Hypersensitivity:** Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma. Hydrochlorothiazide may cause sensitivity reactions or exacerbate/activate systemic lupus erythematosus.

**Use of ACE inhibitors in pregnancy** can cause fetal and neonatal morbidity and mortality. When pregnancy is detected, discontinue VASERETIC® as soon as possible. Rarely, no alternatives to an ACE inhibitor will be found and mothers should be apprised to the potential hazards to the fetus. Serial ultrasounds should be performed to assess fetal development and well-being and volume of amniotic fluid. If oligohydramnios is observed, discontinue VASERETIC® unless lifesaving for the mother. A non-stress test and/or a biophysical profiling may be appropriate; however, if concerns persist, a contraction stress testing should be considered. Oligohydramnios may only appear after fetus has sustained irreversible injury.

Closely observe infants exposed *in utero* to ACE inhibitors for hypotension, oliguria and hyperkalemia, and initiate appropriate corrective medical procedures.

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**Human Data:** Exposure to ACE inhibitors during second and third trimesters has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death of the fetus. Oligohydramnios, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development also has been reported. Prematurity and patent ductus arteriosus also reported but unknown if due to ACE inhibitor use. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

## PRECAUTIONS

**Hyperkalemia:** In clinical trials with enalapril alone, hyperkalemia (K+ >5.7 mEq/L) was observed in approximately 1% of hypertensive patients, and caused discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for hyperkalemia development may include renal insufficiency, diabetes mellitus, and concomitant use of agents to treat hypokalemia (see ADVERSE REACTIONS).

**Valvular Stenosis:** Theoretically, patients with aortic stenosis, who do not develop as much afterload reduction, might be at risk of decreased coronary perfusion when treated with vasodilators.

**Metabolism:** In certain patients, thiazides may cause hyperuricemia or acute gout; decrease serum PBI levels without signs of thyroid disturbances; result in hypomagnesemia; increase cholesterol and triglyceride levels; decrease urinary calcium excretion; and, cause intermittent and slight elevations of serum calcium in absence of known disorders. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Discontinue thiazides before testing for parathyroid function.

**Surgery/Anaesthesia:** During major surgery or anaesthesia with hypotensive agents, enalapril blocks angiotensin II formation secondary to compensatory renin release. Hypotension that develops due to this mechanism can be corrected by volume expansion. Thiazides may increase responsiveness to tubocurarine.

**Cough:** A dry, persistent cough which usually disappears after withdrawal or lowering the dose of enalapril has been reported. Such possibility should be considered as part of the differential diagnosis of the cough.

**Nursing mothers:** Enalapril, enalaprilat and thiazides are secreted in human milk therefore, nursing should be interrupted if VASERETIC® is given to a nursing mother.

**Pediatric use:** Use is not recommended because VASERETIC® has not been studied in children.

**Anaphylactoid Reactions during Membrane Exposure:** Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (eg. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. If symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur, stop dialysis immediately. The symptoms are not relieved by antihistamines and the use of a different type of dialysis membrane or class of antihypertensive agent should be considered.

**Anaphylactoid Reactions during Desensitization:** Isolated reports of sustained life threatening anaphylactoid reactions during desensitizing treatment with hymenoptera (bees, wasp) venom in patients receiving ACE inhibitors. These reactions have been avoided when ACE inhibitors were withheld for 24 hours but have reappeared upon inadvertent rechallenge.

**Drug Interactions**

**Hypotension - Patients on Diuretic Therapy:** Particularly when diuretics recently initiated, patients occasionally experience hypotension after initiating therapy with enalapril. To minimize the hypotensive effects, discontinue the diuretic or increase the salt intake prior to starting the drug (see WARNINGS and DOSAGE AND ADMINISTRATION).

**Agents Increasing Serum Potassium:** Since enalapril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given cautiously for documented hypokalemia only and serum potassium should be monitored frequently. Potassium containing salt substitutes should be used with caution.

**Agents Causing Renin Release:** Diuretics, for example, augment the antihypertensive effect of VASERETIC®.

**Agents Affecting Sympathetic Activity:** Ganglionic blocking agents or adrenergic neuron blocking agents, for example, may be used with caution. Beta-adrenergic blockers add some further antihypertensive effect to enalapril.

**Lithium Salts:** Diuretics decrease lithium clearance and add to risk of lithium toxicity, therefore, do not give with diuretics.

**d-tubocurarine:** Thiazides may increase responsiveness to tubocurarine.

**Insulin:** Requirements may be increased, decreased or unchanged and latent diabetes mellitus may manifest with thiazide use.

**Alcohol, barbiturates, or narcotics:** Potentiation of orthostatic hypotension may occur.

**Corticosteroids, ACTH:** Electrolyte depletion, particularly hypokalemia.

**Pressor amines:** Norepinephrine, for example, may have decreased response but not enough to preclude usage.

**Non-steroidal Anti-inflammatory Drugs:** Co-administration may reduce diuretic, natriuretic and antihypertensive effects of all diuretics; therefore, observe patient closely to ensure desired effect of the diuretic.

## ADVERSE REACTIONS

In clinical trials involving 1580 hypertensive patients, including over 300 patients treated for one year or more, the most severe adverse reactions were angioedema (0.3%), syncope (1.3%) and renal failure (0.1%). The most frequent clinical adverse reactions in controlled clinical trials were: dizziness (8.6%), headache (5.5%), fatigue (3.9%) and cough (3.5%). Reported adverse experiences have been previously reported for both enalapril and hydrochlorothiazide when used separately.

Adverse reactions occurring in patients treated with VASERETIC® in controlled trials are shown below.

| | Enalapril (2314 Patients) (%) | Enalapril + hydrochlorothiazide (1580 Patients) (%) |
|---|---|---|
| **CARDIOVASCULAR** | | |
| Hypotension | 0.9 | 0.9 |
| Chest Pain | 0.9 | 1.1 |
| Palpitations | 0.6 | 1.0 |
| Syncope | 0.5 | 1.3 |
| Myocardial Infarction | 0.2 | 0.4 |
| **GASTROINTESTINAL** | | |
| Nausea | 1.4 | 2.5 |
| Vomiting | 0.8 | 1.6 |
| Dysphagia | 0.1 | 0.1 |
| Diarrhea | 1.4 | 2.1 |
| Abdominal pain | 0.7 | 1.1 |
| **RENAL** | | |
| Renal failure | 0.1 | 0.1 |
| Oliguria | 1 case | 2 cases |
| Proteinuria† | 0.1 | 0 |
| **DERMATOLOGIC** | | |
| Rash | 1.4 | 1.3 |
| Pruritus | 0.4 | 0.5 |
| **NERVOUS SYSTEM** | | |
| Headache | 5.2 | 5.5 |
| Dizziness | 4.3 | 8.6 |
| Insomnia | 0.5 | 0.9 |
| Nervousness | 0.6 | 0.5 |
| Somnolence | 0.6 | 0.5 |
| Paresthesia | 0.6 | 1.1 |
| **ALLERGIC** | | |
| Cough | 1.3 | 3.5 |
| Angioedema | 0.2 | 0.3 |
| **HEMATOLOGIC** | | |
| Anemia | 0.1 | 0.1 |
| Leukopenia | 1 case | 0 |
| **MISCELLANEOUS** | | |
| Muscle cramps | 0.6 | 2.7 |
| Dyspnea | 0.6 | 0.7 |
| Hyperhidrosis | 0.7 | 0.8 |
| Impotence | 0.4 | 2.2 |
| Fatigue | 3.0 | 3.9 |
| Taste disturbance | 0.4 | 0.2 |

† Defined as > 1g/24h or >0.5 g/12h on two consecutive measurements, at least one month apart.

**ABNORMAL LABORATORY FINDINGS**

**Hyperkalemia:** (see PRECAUTIONS).

**Creatinine, Blood Urea Nitrogen:** Increases, which were reversible upon discontinuation of therapy, were reported in about 0.6% of patients with essential hypertension treated with VASERETIC®, and if enalapril used alone, 20% of patients with renovascular hypertension and about 0.2% of patients with essential hypertension. Increases were reversible upon discontinuation of therapy.

**Hemoglobin and Hematocrit:** Decreases (mean approximately 0.34 g% and 1.0 vol%, respectively) occurred frequently in hypertensive patients treated with enalapril maleate, but were rarely of clinical importance. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

**Others:** Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS).

**ADVERSE REACTIONS REPORTED IN UNCONTROLLED TRIALS AND/OR MARKETING EXPERIENCE**

**VASOTEC®**
**With an incidence of 0.5 to 1%:**
Insomnia, impotence, renal dysfunction, renal failure and oliguria.

**With an incidence < 0.5%:**
**Cardiovascular:** Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS); cardiac arrest; pulmonary embolism; rhythm disturbances; angina pectoris. **Gastrointestinal:** Anorexia; ileus; pancreatitis; dyspepsia; constipation. **Hemopoeitic:** Neutropenia; thrombocytopenia; bone marrow depression. **Hepatic:** Liver function abnormalities; hepatitis; jaundice (hepatocellular and/or cholestatic). **Nervous System/Psychiatric:** Vertigo; depression; confusion; ataxia. **Respiratory:** Bronchospasm/asthma; rhinorrhea. **Other:** Erythema multiforme; exfoliative dermatitis; Stevens-Johnson syndrome; toxic epidermal necrosis; urticaria; photosensitivity; alopecia; flushing; tinnitus; hearing impairment; glossitis; blurred vision. A symptom complex has been reported which may include fever, serositis, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

**LABORATORY TEST FINDINGS:** Hyponatremia

**VASERETIC® (Marketing Experience Only):** Arthralgia, asthenia, constipation, decreased libido, dry mouth, dyspepsia, flatulence, gout, hypotension, tachycardia, tinnitus, and vertigo.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific information is available on the treatment of overdosage with VASERETIC®. Treatment is symptomatic and supportive. Discontinue VASERETIC® and observe closely. Suggested measures include induction of emesis and/or gastric lavage, correction of dehydration, electrolyte balance and hypotension by established procedures. Enalaprilat may be removed from the general circulation by hemodialysis.

**Enalapril maleate:** The most prominent feature of overdosage is marked hypotension beginning approximately 6 hours after ingestion, concomitant with blockade of renin-angiotensin system and stupor. Serum enalaprilat levels 100 and 200 times higher than usually seen after therapeutic doses have occurred with ingestion of 300 mg and 440 mg of enalapril, respectively.

**Hydrochlorothiazide:** Electrolyte depletion and dehydration are the most common signs and symptoms. If digitalis given concomitantly, hypokalemia may cause cardiac arrhythmias.

## DOSAGE AND ADMINISTRATION

**Dosage must be individualized. Fixed combination is not for initial therapy and dosage must be determined by titration of individual components.**

After successful titration described below, VASERETIC® may be substituted if dose and schedule can be achieved with combination. (See INDICATIONS and WARNINGS)

Particularly when combined with hypertensive agents, patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily; therefore daily dosage of VASERETIC® should not exceed 2 tablets. Consider increasing enalapril or other non-diuretic if further reduction of blood pressure is required.

The recommended initial dose of enalapril in patients not on diuretics is 5 mg once a day. Adjust dosage according to blood pressure response; the usual range is 10 to 40 mg daily, in a single dose or divided in two doses. Some patients on once-daily dosage may have diminished antihypertensive effect toward the end of dosing interval and require an increase in dosage, or twice daily administration. If blood pressure is not controlled, a diuretic may be added. In the elderly the starting dose of enalapril should be 2.5 mg since some elderly patients may be more responsive.

Symptomatic hypotension may occasionally occur following the initial dose of enalapril, more likely in patients currently taking a diuretic. Therefore, if possible, discontinue the diuretic two to three days before initiating enalapril therapy (see WARNINGS). If the diuretic cannot be discontinued, use an initial dose of 2.5 mg.

Titrate individual components in patients with mild to moderate renal impairment (creatinine clearance >30 mL/min). The usual starting dose for enalapril alone in mildly impaired patients is 5 mg and 2.5 mg in moderately impaired patients. When concomitant diuretics therapy required in patients with severe renal impairment, give a loop diuretic instead of a thiazide diuretic. Therefore, VASERETIC® is not recommended for patients with severe renal dysfunction. (see PRECAUTIONS-Anaphylactoid Reactions during Membrane Exposure).

## AVAILABILITY OF DOSAGE FORMS

Each red, squared capsule-shaped, compressed tablets, engraved 720 on one side and VASERETIC on other, contain 10 mg of enalapril maleate and 25 mg of hydrochlorothiazide.

Available in blisters of 30.

## PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(496x-a,9,93)

### Reference


1. Vidt D. A controlled multiclinic study to compare the antihypertensive effects of MK-421, hydrochlorothiazide, and MK-421 combined with hydrochlorothiazide in patients with mild to moderate essential hypertension. J Hypertens 1984;2(Suppl 2):81-88.


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DIV. OF MERCK FROSST CANADA INC.
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# P Plendil® ONCE•A•DAY

FELODIPINE EXTENDED RELEASE TABLETS

**Vascular selective – hypertension specific**

2.5 mg, 5 mg and 10 mg

**Antihypertensive Agent/Dihydropyridine Calcium Channel Blocker**

### INDICATIONS AND CLINICAL USE

PLENDIL® (felodipine) is indicated in the treatment of mild to moderate essential hypertension. PLENDIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

PLENDIL can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Combination of PLENDIL with a thiazide diuretic or a beta-blocker has been found to be compatible and showed an additive anti-hypertensive effect. Safety and efficacy of concurrent use of PLENDIL with other antihypertensive agents has not been established.

### CONTRAINDICATIONS

PLENDIL (felodipine) is contraindicated in:

1) Patients with a known hypersensitivity to felodipine or other dihydropyridines.
2) In women of childbearing potential, in pregnancy, and during lactation. Fetal malformations and adverse effects on pregnancy have been reported in animals.

**Teratogenic Effects.** Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomologus monkeys, no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

**Non-teratogenic Effects.** In a study on fertility and general reproductive performance in rats, prolongation of parturition with difficult labour and an increased frequency of fetal and early postnatal deaths were observed in the groups treated with doses of 9.6 mg/kg/day and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day. This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

### WARNINGS

**Congestive Heart Failure.** The safety and efficacy of PLENDIL (felodipine) in patients with heart failure has not been established. Caution should, therefore, be exercised when using PLENDIL in hypertensive patients with compromised ventricular function, particularly in combination with a beta-blocker. Acute hemodynamic studies in a small number of patients with New York Heart Association Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects.

**Hypotension, Myocardial Ischemia.** PLENDIL may, occasionally, precipitate symptomatic hypotension and rarely syncope. It may lead to reflex tachycardia which, particularly in patients with severe obstructive coronary artery disease, may result in myocardial ischemia. Careful monitoring of blood pressure during the initial administration and titration of felodipine is recommended. Care should be taken to avoid hypotension especially in patients with a history of cerebrovascular insufficiency, and in those taking medications known to lower blood pressure.

**Beta-Blocker Withdrawal.** PLENDIL gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blockers.

**Outflow Obstruction.** PLENDIL should be used with caution in the presence of fixed left ventricular outflow obstruction.

### PRECAUTIONS

**Peripheral Edema.** Mild to moderate peripheral edema was the most common adverse event in the clinical trials. The incidence of peripheral edema was dose-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

**Use in Elderly Patients or in Patients with Impaired Liver Function.** Patients over 65 years of age as well as patients with impaired liver function may have elevated plasma concentrations of felodipine and, therefore, may require lower doses of PLENDIL. These patients should have their blood pressure monitored closely during the initial administration and dosage adjustment of PLENDIL, and should rarely require doses above 10 mg per day. (See Pharmacokinetics and DOSAGE AND ADMINISTRATION.)

**Gingival Hyperplasia.** PLENDIL can induce gingival enlargement in patients with pronounced gingivitis and parodontitis. However, such changes may be reversed by measures of good oral hygiene and mechanical debridement of the teeth.

**Pregnancy and Lactation.** See CONTRAINDICATIONS.

**Use in Children.** PLENDIL is not recommended in children since the safety and efficacy in children have not been established.

**Drug Interactions.** *Beta-Adrenoceptor Blocking Agents:* A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and $C_{max}$ of metoprolol, however, were increased approximately 31 and 36 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

*Cimetidine:* In healthy volunteers pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the $C_{max}$ of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

*Digoxin:* When given concomitantly with felodipine as conventional tablets the peak plasma concentration of digoxin was significantly increased. With the extended release formulation of felodipine there was no significant change in peak plasma levels or AUC of digoxin.

*Phenytoin, carbamazepine and phenobarbital:* In a pharmacokinetic study maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long term anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in healthy volunteers. The mean area under the felodipine plasma concentration-time curve was also reduced in epileptic patients to approximately 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

**Other Concomitant Therapy:** In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

### ADVERSE REACTIONS

In 1102 patients treated with felodipine, either alone or in combination with other antihypertensive agents, adverse events were reported in 52% of patients and caused discontinuation of therapy in 9%. The most common adverse events (incidence of at least 1%) were: peripheral edema (21.3%), headache (14.9%), feeling of warmth/flush (13.2%), dizziness/vertigo (4.6%), fatigue (2.4%), palpitation (1.6%), extrasystoles (1.5%), nausea (1.5%), pain (1.5%), paraesthesia (1.2%), chest pain (1.1%).

In addition, the following events were reported with an incidence of less than 1 percent (Adverse Events that were Judged Serious are in Bold Face): *Cardiovascular:* **angina pectoris**, **myocardial infarction**, **atrial fibrillation**, arrhythmia, abnormal ECG, AV block, bundle branch block, postural hypotension, syncope, tachycardia, bradycardia. *Central & Peripheral Nervous System:* **brain stem disorder**, tremor, abnormal gait, anxiety, depression, insomnia, nervousness, somnolence, agitation, apathy, increased appetite, impaired concentration, confusion, emotional lability, hallucination, sleep disorder, malaise. *Gastrointestinal:* **abnormal hepatic function**, cholestatic hepatitis, abdominal pain, vomiting, constipation, diarrhea, dyspepsia, dysphagia, flatulence, gingivitis, gum hyperplasia, gingival bleeding, dry mouth, salivary gland enlargement. *Dermatologic:* photosensitivity reaction, erythema nodosum, eczema, pruritus, rash, increased sweating. *Musculo-skeletal:* arthralgia, myalgia. *Respiratory:* cough, dyspnea. *Genito-urinary:* impotence, dysuria, frequent urination. *Others:* abnormal vision, anemia, substernal chest pain, asthenia, generalized edema, periorbital edema, facial edema, change in weight, chills.

*Laboratory tests:* For the following laboratory values statistically significant decreases were observed; bilirubin, red blood count, hemoglobin, and urate. Statistically significant increases were found in erythrocyte sedimentation rate and thrombocyte count. None of these changes were considered to be of clinical significance.

In addition, the following abnormal blood chemistry results were reported: hypokalemia, hyperkalemia, hyponatremia.

### DOSAGE AND ADMINISTRATION

PLENDIL should be swallowed whole and not crushed or chewed.

The dose should be adjusted individually according to patient response.

The recommended initial dose is 5 mg once daily. The 2.5 mg tablet is available for dose titration purposes. The usual maintenance dosage range is 5-10 mg once daily. Dose adjustment, if necessary, should be done at intervals of not less than two weeks. The maximum recommended daily dose is 20 mg once a day. In clinical trials 20 mg once daily showed an increased blood pressure response but also a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment. Plendil tablets are extended release, film-coated tablets, containing felodipine in strengths of 2.5 mg, 5 mg and 10 mg.

**Use in the Elderly or in Patients with Impaired Liver Function.** Patients over 65 years of age or patients with impaired liver function, may have elevated plasma concentrations of felodipine (see PRECAUTIONS). In these patients an initial treatment of 2.5 mg daily should be considered. In general, doses above 10 mg should not be considered in these patients.

Product monograph available on request.


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ASTRA


Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

# Luvox*

fluvoxamine maleate
film coated tablets
Antidepressant
Antiobsessional Agent

**ACTION:** The antidepressant and antiobsessional actions of fluvoxamine are believed to be related to its selective inhibition of presynaptic serotonin re-uptake in brain neurons.

There is minimum interference with noradrenergic processes, and, in common with several other specific inhibitors of serotonin uptake, fluvoxamine has very little *in vitro* affinity for $\alpha 1$, $\alpha 2$, $\beta 1$, dopamine$_2$, histamine$_1$, serotonin$_1$, serotonin$_2$ or muscarinic receptors.

**Pharmacokinetics:** In healthy volunteers, fluvoxamine is well absorbed after oral administration. Following a single 100 mg oral dose, peak plasma levels of 31-87 ng/mL were attained 1.5 to 8 hours post-dose. Peak plasma levels and AUC's (0-72 hours) are directly proportionate to dose after single oral doses of 25, 50, and 100 mg.

Following single doses, the mean plasma half-life is 15 hours, and slightly longer (17-22 hours), during repeated dosing. Steady-state plasma levels are usually achieved within 10-14 days. The pharmacokinetic profile in the elderly is similar to that in younger patients.

**Metabolism and Elimination:** Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, to at least nine metabolites, which are excreted by the kidney. Ninety-four percent of an oral radioactive dose is recovered in the urine within 48 hours. The two major metabolites showed negligible pharmacological activity. *In vitro* binding of fluvoxamine to human plasma proteins is about 77% at drug concentrations up to 4000 ng/mL.

**INDICATIONS: Depression:** LUVOX (fluvoxamine) may be indicated for the symptomatic relief of depressive illness.

The effectiveness of fluvoxamine in long-term use (i.e., for more than 5 to 6 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use fluvoxamine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

**Obsessive-Compulsive Disorder:** LUVOX (fluvoxamine) has been shown to significantly reduce the symptoms of obsessive-compulsive disorder. The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming, or interfering significantly with the person's social or occupational functioning.

The efficacy of LUVOX (fluvoxamine) has been studied in double-blind, placebo-controlled clinical trials conducted in obsessive-compulsive outpatients. The usefulness of LUVOX (fluvoxamine) for long-term use (i.e. for more than 10 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use LUVOX (fluvoxamine) for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

**CONTRAINDICATIONS:** LUVOX (fluvoxamine) is contraindicated in patients with known hypersensitivity to the drug.

Fluvoxamine should not be administered together with monoamine oxidase (MAO) inhibitors. At least two weeks should elapse after discontinuation of MAO inhibitor therapy before fluvoxamine treatment is initiated. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with LUVOX (fluvoxamine).

**PRECAUTIONS: Seizures:** Convulsions have been reported rarely during LUVOX (fluvoxamine) administration. Caution is recommended when the drug is administered to patients with a history of seizures. If seizures occur during fluvoxamine administration, the drug should be discontinued.

**ECT:** Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

**Hepatic Enzymes:** Treatment with fluvoxamine has been rarely associated with increases in hepatic enzymes, usually accompanied by symptoms. Fluvoxamine administration should be discontinued in such cases.

**Combination with Alcohol:** Fluvoxamine may potentiate the effects of alcohol and increase the level of psychomotor impairment.

**Cognitive and Motor Disturbances:** Sedation may occur in some patients. Therefore, patients should be cautioned about participating in activities requiring complete mental alertness, judgement, and physical co-ordination – such as driving an automobile or performing hazardous tasks – until they are reasonably certain that treatment with LUVOX (fluvoxamine) does not affect them adversely.

**Suicide:** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high-risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for LUVOX (fluvoxamine) should be written for the smallest quantity of drug consistent with good patient management.

**Concomitant Illness:** LUVOX (fluvoxamine) has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from premarketing clinical studies.

**Use in Pregnancy and Lactation:** Safe use of fluvoxamine during pregnancy and lactation has not been established. Therefore, it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus.

**Use in Children:** Safety and efficacy in children under 18 years of age have not been established.

**Drug Interactions:** Combined use of LUVOX (fluvoxamine) and MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

An increase in tricyclic antidepressant blood levels has also been reported in patients taking fluvoxamine concomitantly.

Lithium, and possibly tryptophan, may enhance the serotonergic effects of fluvoxamine; these combinations should therefore be used with caution.

Fluvoxamine may prolong the elimination of drugs which are metabolized by oxidation in the liver, and a clinically significant interaction is more likely when the second agent has a narrow therapeutic index, as is the case with warfarin, phenytoin, and theophylline. Such combinations should therefore be administered with caution, and consideration be given to lowering the dose of the second agent. In interaction studies, a 5-fold increase in plasma levels of propranolol and a 65% increase in warfarin plasma levels were seen during concurrent administration of fluvoxamine. An absence of pharmacokinetic interaction has been seen with digoxin and atenolol, which are not significantly metabolized in the liver.

**Cytochrome P450 Isozyme (IID6):** Like other selective serotonin reuptake inhibitors, fluvoxamine inhibits the specific hepatic cytochrome P450 isozyme (IID6) which is responsible for the metabolism of debrisoquine and sparteine. Although the clinical significance of this effect has not been established, inhibition of IID6 may lead to elevated plasma levels of co-administered drugs which are metabolized by this isozyme. Drugs metabolized by cytochrome P450IID6 include the tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (e.g., perphenazine and thioridazine), and Type 1C antiarrhythmics (e.g., propafenone and flecainide).

**ADVERSE REACTIONS: Commonly Observed:** In clinical trials, the most commonly observed adverse events associated with LUVOX (fluvoxamine) administration, and not seen at an equivalent incidence among placebo-treated patients, were gastrointestinal complaints, including nausea (sometimes accompanied by vomiting), constipation, anorexia, diarrhea and dyspepsia; central nervous system complaints, including somnolence, dry mouth, nervousness, insomnia, dizziness, tremor and agitation; and asthenia. Abnormal (mostly delayed) ejaculation was frequently reported by patients with obsessive compulsive disorder, primarily at doses over 150 mg/day.

**Adverse Events Leading to Discontinuation of Treatment:** Fifteen percent of approximately 25,000 patients who received LUVOX (fluvoxamine) in clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials included nausea and vomiting, insomnia, agitation, headache, abdominal pain, somnolence, dizziness, asthenia and anorexia. The most common events causing discontinuation in patients suffering from obsessive compulsive disorder included insomnia, asthenia and somnolence.

**Incidence of Adverse Experiences:** Adverse events with an incidence of ≥ 5% reported in double-blind, placebo-controlled clinical trials in depression and in obsessive compulsive disorder are presented in the following table for each indication.

**TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE (≥ 5%) IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR DEPRESSION AND OBSESSIVE COMPULSIVE DISORDER***

| Percentage of Patients Reporting Event | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Depression | | OCD | | | Depression | | OCD | |
| Body System/ Adverse Event | Fluvoxamine (N=222) | Placebo (N=192) | Fluvoxamine (N=160) | Placebo (N=160) | Body System/ Adverse Event | Fluvoxamine (N=222) | Placebo (N=192) | Fluvoxamine (N=160) | Placebo (N=160) |
| **Nervous System** | | | | | **Body as a Whole** | | | | |
| Somnolence | 26.2 | 9.0 | 26.9 | 9.4 | Headache | 21.6 | 18.7 | 20.0 | 23.8 |
| Agitation | 15.7 | 8.9 | 3.8 | 0 | Pain | 5.9 | 3.7 | 4.4 | 1.3 |
| Insomnia | 14.4 | 10.4 | 31.3 | 15.0 | Asthenia | 4.9 | 3.2 | 28.8 | 9.4 |
| Dizziness | 14.8 | 13.5 | 9.4 | 4.4 | Infection | - | - | 11.3 | 9.4 |
| Tremor | 10.8 | 4.7 | 8.1 | 0.6 | Abdominal Pain | 3.6 | 3.6 | 5.6 | 8.1 |
| Hypokinesia | 8.1 | 3.6 | - | - | Flu Syndrome | - | - | 5.0 | 3.8 |
| Hyperkinesia | 6.7 | 8.9 | - | - | | | | | |
| Depression | 4.0 | 4.2 | 6.3 | 4.4 | **Skin** | | | | |
| Nervousness | 2.2 | 1.6 | 15.6 | 5.0 | Sweating Increased | 11.2 | 12.5 | 6.9 | 1.9 |
| Anxiety | 2.3 | 2.1 | 9.4 | 6.9 | | | | | |
| Libido Decreased | - | - | 7.5 | 1.9 | **Respiratory System** | | | | |
| Thinking Abnormal | - | - | 6.9 | 3.8 | Pharyngitis | - | - | 6.3 | 5.0 |
| | | | | | Rhinitis | 1.3 | 2.6 | 5.6 | 1.9 |
| **Digestive System** | | | | | | | | | |
| Nausea | 36.5 | 10.9 | 28.8 | 6.9 | **Special Senses** | | | | |
| Dry Mouth | 25.7 | 23.9 | 11.9 | 3.1 | Accommodation Abnormal | 6.3 | 6.3 | - | - |
| Constipation | 18.0 | 6.8 | 14.4 | 8.8 | Taste Perversion | 3.2 | 3.1 | 5.0 | 0 |
| Anorexia | 14.9 | 6.3 | 5.0 | 3.1 | | | | | |
| Diarrhea | 5.9 | 6.3 | 11.9 | 8.8 | **Urogenital** | | | | |
| Dyspepsia | 3.2 | 0 | 13.8 | 9.4 | Urinary Frequency | 2.2 | 1.6 | 5.0 | 1.3 |
| | | | | | Abnormal Ejaculation | 1.4 | 0 | 17.9+ | 0 |

*Dosage titration at study initiation varied between the depression and OCD trials. In depression, fluvoxamine was administered: Day 1, 50 mg hs; Day 2, 100 mg; Day 3, 150 mg then titrated to response. In OCD, fluvoxamine was administered: Days 1-4, 50 mg; Days 5-8, 100 mg, Days 9-14, 150 mg then titrated to response.

+Corrected for gender (males: n=78)

During premarketing and postmarketing studies, multiple doses of LUVOX (fluvoxamine) were administered to approximately 25,000 patients. All events with an incidence of > 0.01% are listed, regardless of relation to drug, except those in terms so general as to be uninformative. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent (occurring on 1 or more occasions in at least 1/100 patients), infrequent (occurring in less than 1/100, but at least 1/1000 patients), or rare (occurring in less than 1/1000 but at least in 1/10,000 patients). Multiple events may have been reported by a single patient. It is important to emphasize that although the events reported did occur during treatment with LUVOX (fluvoxamine), they were not necessarily caused by it.

**Nervous System:** *Frequent:* Somnolence, dry mouth, insomnia, dizziness, nervousness, tremor, vertigo, thinking abnormal, agitation, anxiety, amnesia, depression. *Infrequent:* Abnormal dreams, paraesthesia, vasodilatation, libido decreased, depersonalization, psychotic depression, hypertonia, confusion, apathy, emotional lability, ataxia, abnormal gait, hostility, hyperkinesia, libido increased, hypokinesia, euphoria, neurosis, incoordination, hypesthesia, increased salivation. *Rare:* Screaming syndrome, hypotonia, hemiplegia, hallucinations, akathisia, manic reaction, myoclonus, twitching, drug dependence, stupor, delirium, convulsion, neuralgia, dysarthria, paranoid reaction, extrapyramidal syndrome, neuropathy, CNS neoplasia, akinesia, dyskinesia, paralysis, psychosis, CNS stimulation, coma, delusions, hyperesthesia, hysteria, schizophrenic reaction, torticollis, trismus, dystonia, reflexes decreased.

**Digestive System:** *Frequent:* Nausea, vomiting, dyspepsia, constipation, diarrhea, anorexia. *Infrequent:* Flatulence, dysphagia, increased appetite, eructation, thirst, colitis. *Rare:* Gastroenteritis, gastritis, stomatitis, glossitis, hepatitis, esophagitis, fecal incontinence, gingivitis, jaundice, mouth ulceration, rectal hemorrhage, melena, tongue discoloration, tooth disorder, biliary pain, gastrointestinal carcinoma, gastrointestinal hemorrhage, hematemesis, liver function tests abnormal, tenesmus, tongue edema.

**Cardiovascular System:** *Frequent:* Palpitation. *Infrequent:* Syncope, tachycardia, postural hypotension, hypotension, migraine, hypertension. *Rare:* Angina pectoris, arrhythmia, myocardial infarct, pallor, bradycardia, extrasystoles, hemorrhage, peripheral vascular disorder, cerebrovascular accident, shock.

**Body as a Whole:** *Frequent:* Asthenia, headache, abdominal pain, malaise, pain. *Infrequent:* Back pain, chills, chest pain, suicide attempt, fever, neck pain, infection, allergic reaction, accidental injury, flu syndrome. *Rare:* Overdose, face edema, hangover effect, abdomen enlarged, halitosis, neck rigidity, pelvic pain, hernia, chills and fever.

**Skin:** *Frequent:* Sweating increased. *Infrequent:* Pruritus, rash. *Rare:* Urticaria, acne, eczema, dry skin, alopecia, psoriasis, furunculosis, Herpes simplex, Herpes zoster, maculopapular rash.

**Respiratory System:** *Infrequent:* Dyspnea, pharyngitis, rhinitis. *Rare:* Cough increased, yawn, epistaxis, hyperventilation, sinusitis, bronchitis, laryngismus, hiccup, pneumonia, asthma, laryngitis, voice alternation.

**Special Senses:** *Infrequent:* Taste perversion, tinnitus, amblyopia, abnormal vision, hyperacusis. *Rare:* Conjunctivitis, abnormality of accommodation, taste loss, eye pain, lacrimation disorder, diplopia, dry eyes, mydriasis, ear pain, parosmia, deafness, photophobia, blepharitis.

**Musculoskeletal System:** *Infrequent:* Myalgia, arthralgia, myasthenia, tetany. *Rare:* Leg cramps, arthrosis, rheumatoid arthritis, arthritis, bone pain, pathological fracture.

**Urogenital System:** *Infrequent:* Urinary frequency, impotence, dysuria, metrorrhagia, abnormal ejaculation. *Rare:* Urinary incontinence, breast pain, urinary retention, urinary urgency, cystitis, nocturia, menorrhagia, anorgasmia, female lactation, vaginitis, amenorrhea, dysmenorrhea, urinary tract infection, hematuria, kidney pain, prostatic disorder, polyuria, leukorrhea.

**Metabolic and Nutritional System:** *Frequent:* Weight gain. *Infrequent:* Weight loss, peripheral edema. *Rare:* Alcohol intolerance, dehydration, obesity, edema

**Hematic and Lymph Systems:** *Rare:* Ecchymosis, cyanosis, anemia, lymphadenopathy, thrombocytopenia.

**SYMPTOMS AND TREATMENT OF OVERDOSE:**

**Symptoms:** More than 300 cases of overdosage with fluvoxamine, alone or in combination with other compounds, have been reported. The most common symptoms of overdosage include gastrointestinal complaints (nausea, vomiting, and diarrhoea), somnolence, and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions, and coma have also been reported. Among 300 patients reported to have taken deliberate overdoses of fluvoxamine, there have been 15 deaths, all but one of which occurred in patients who were confirmed to have taken multiple medications.

**Treatment:** There is no specific antidote to fluvoxamine. In situations of overdosage, the stomach should be emptied as soon as possible after tablet ingestion and symptomatic treatment initiated. The repeated use of medicinal charcoal is also recommended. Due to the large distribution volume of fluvoxamine, forced diuresis or dialysis is unlikely to be of benefit. The highest documented dose of fluvoxamine ingested by a patient is 9000 mg; this patient recovered completely with symptomatic treatment only.

**DOSAGE AND ADMINISTRATION: Depression:** ***Adult Dosage:*** Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime, and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 200 mg, and should be adjusted gradually according to the individual response of the patient, up to a maximum of 300 mg. Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose. Tablets should be swallowed with water and without chewing.

**Obsessive Compulsive Disorder:** Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime, and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 300 mg, and should be adjusted gradually according to the individual response of the patient, up to a maximum of 300 mg. If no improvement is observed within 10 weeks, treatment with LUVOX (fluvoxamine) should be reconsidered.

Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose. LUVOX (fluvoxamine) should be swallowed with water and without chewing.

**Use In Hepatic or Renal Insufficiency:** Patients with hepatic or renal insufficiency should begin treatment with a low dose and be carefully monitored.

**Use In Children:** The safety and effectiveness of fluvoxamine in children under 18 years of age have not been established.

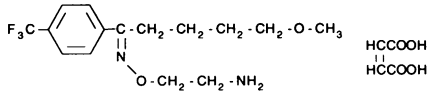
**Use In Geriatrics:** Since there is limited clinical experience in the geriatric age group, caution is recommended when administering fluvoxamine to elderly patients.

**PHARMACEUTICAL INFORMATION: Drug Substance:**

*Proper Name:* Fluvoxamine maleate

*Chemical Name:* 5-methoxy-4'-(trifluoromethyl) valerophenone(E)-0-(2-aminoethyl) oxime maleate (1:1)

*Structured Formula:*




*Molecular Weight:* 434.4

*Description:* White, odorless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

**Storage Conditions:** Preserve in well-closed containers. Store in a dry place at temperatures not below 0°C and not above 30°C.

**AVAILABILITY:** Each round, yellow, 50 mg tablet, stamped "291" on one side and "DUPHAR" on the other, contains 50 mg fluvoxamine maleate. Bottles of 50.

Each oval, yellow, 100 mg tablet, stamped "313" on one side and "DUPHAR" on the other, contains 100 mg fluvoxamine maleate. Bottles of 50.

Fluvoxamine is a Schedule F drug.

**REFERENCES**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Complete Product Monograph available to physicians and pharmacists upon request.

Direct medical information enquiries to; McNeil Pharmaceutical, Medical Information.


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# Luvox*
fluvoxamine maleate

CAN HELP WITH LESS HURT

# ℙ DICETEL®

(Pinaverium Bromide)
50 mg film-coated tablets

**NAME OF DRUG:** DICETEL® (Pinaverium Bromide) 50 mg film-coated tablets

**THERAPEUTIC CLASSIFICATION:** Gastrointestinal calcium antagonist

**CLINICAL PHARMACOLOGY:** Pinaverium bromide is a calcium antagonist which inhibits the calcium influx by blocking the voltage-dependent calcium channel at the smooth muscle cell level. It possesses a high degree of selectivity for the intestinal smooth muscle.[5,7,19,32,36,48,50] Many studies showed that pinaverium bromide induces a relaxation of the gastrointestinal and the biliary tracts and mainly of the colon, an inhibition of the motor colonic response to food and/or pharmacological stimulations, implying the action of the drug in irritable bowel syndrome.[4,9,37,47]

**INDICATIONS AND CLINICAL USE:** DICETEL is indicated:
– for the treatment and relief of symptoms associated with irritable bowel syndrome (IBS): abdominal pain, bowel disturbances and intestinal discomfort.
– for the treatment of symptoms related to functional disorders of the biliary tract.

**CONTRAINDICATIONS:** DICETEL is contraindicated in patients with known hypersensitivity to pinaverium bromide or any of the excipients. No other contraindications have been identified at this time.

**WARNINGS:** Contact of pinaverium bromide with the oesophageal mucosa may be irritating. Therefore, it is strongly recommended that the tablet be taken with a glass of water during mealtime. If more than three tablets are prescribed per day, the additional tablet(s) should be taken concurrently with a glass of water and a snack.

**PRECAUTIONS:** DICETEL should not be administered for the relief of motility dysfunction due to underlying organic disease.

**Use in pregnancy:**[3] Reproductive studies performed in animals have not revealed the presence of teratogenic effects. However, the safety of **DICETEL** during pregnancy has not been established. Consequently, in the pregnant patient, this drug should only be administered if, in the judgement of the physician, its use is essential to the welfare of the patient.

**Use during lactation:** There have been no controlled studies in nursing women, therefore, the drug should be avoided during lactation.

**ADVERSE REACTIONS:** Minor adverse events were reported and listed as mild and moderate. They were mainly minor digestive disorders that may be related to the disease, such as epigastric pain and/or fullness (0.8%), nausea (0.5%), constipation (0.4%), heartburn (0.3%), distension (0.3%), diarrhoea (0.2%).[8]
For other systems: headache (0.3%), dryness of the mouth (0.3%), drowsiness (0.2%), vertigo (0.2%) and skin allergy (0.2%).

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** In man, apart from diarrhoea and/or flatulence, pinaverium bromide induced no undesirable effects in daily dosages of up to 1,200 mg.[41,42]
No cases of overdosage of DICETEL have been reported to date. However, if overdosage occurs, gastric lavage is recommended and symptomatic treatment initiated if deemed necessary.

**DOSAGE AND ADMINISTRATION:** The usual adult dosage is three film-coated tablets of 50 mg a day (one tablet three times a day). In exceptional cases, the dosage may be increased up to six tablets a day (two tablets three times a day).
It is recommended that the tablet be taken with a glass of water during meals or snacks. The tablet should not be swallowed when in the lying position or just before bedtime.
The duration of treatment depends on the disorders for which DICETEL is given.

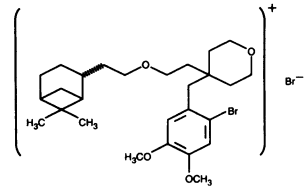
**AVAILABILITY:** DICETEL is available as:

**Tablets:** DICETEL 50 mg: Each orange-coloured, circular-shaped, film-coated tablet with a slightly convex surface contains 50 mg of pinaverium bromide as active ingredient. Available in blister packs, in boxes of 100 tablets.

**PHARMACEUTICAL INFORMATION**
**DRUG SUBSTANCE**
**CHEMISTRY:**

**Structural Formula and Chemistry:** The chemical name for DICETEL (pinaverium bromide) is 4-(6-bromoveratryl)-4-[2-[2-(6,6-dimethyl-2-norpinyl)ethoxy]ethyl]-morpholinium bromide.

**Structural formula:**



**Molecular formula:** $C_{26}H_{41}Br_2NO_4$

**Molecular weight:** 591.42

**Description:** Pinaverium bromide is a white, fine, crystalline powder, poorly soluble in distilled water, practically insoluble in ether, but very soluble in 96% alcohol. The melting range determined by means of Mettler FP apparatus is 152° to 158°C.

**Stability and storage recommendations:** The stability of DICETEL film-coated tablets has been demonstrated in blister packaging alone and in blister packs inserted in the dispensing box. DICETEL should be stored at room temperature (15°C to 30°C) in its dispensing box.

**COMPOSITION**

**Tablets:** In addition to pinaverium bromide, DICETEL contains the following excipients:

– *in the core:* microcrystalline cellulose, modified corn starch, modified lactose, hydrophobic anhydrous silica, talc and magnesium stearate;

– *in the film coating:* gastrosoluble acrylic resin, micronized talc, polyoxyethylene glycol 6000, Sepisperse orange K3020 [titanium dioxide (E 171), sunset yellow lake (E 110), hydroxy propylcellulose (E 463)];

– *intermediary solvents:* ethanol, isopropanol and acetone.

**REFERENCES:**


1. Dicetel Product Monograph, Solvay Kingswood Inc. 1993.
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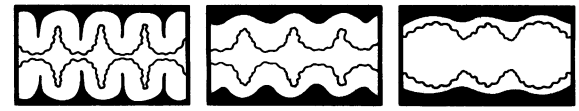
PAAB CCPP

ℙ Dicetel®

PINAVERIUM BROMIDE



The GI calcium antagonist.

PRESCRIBING INFORMATION

# CIPRO®

CIPROFLOXACIN HYDROCHLORIDE THERAPEUTIC CLASSIFICATION ANTIBACTERIAL AGENT

## INDICATIONS AND CLINICAL USES

CIPRO® (Ciprofloxacin hydrochloride tablets) may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

**Respiratory Tract Infections:** Acute exacerbations of chronic bronchitis caused by: *H. influenzae, M. catarrhalis, S. pneumoniae*
Acute pneumonia caused by: *E. cloacae, E. coli, H. influenzae, K. pneumoniae, P. mirabilis, P. aeruginosa, S. aureus, S. pneumoniae*
Due to the nature of the underlying conditions which usually predispose patients to *Pseudomonas* infections of the respiratory tract, bacterial eradications may not be achieved in patients who display clinical improvement despite evidence of *in vitro* sensitivity. In patients requiring subsequent courses of therapy, CIPRO® should be used alternately with other antipseudomonal agents. Some strains of *Pseudomonas aeruginosa* may develop resistance during treatment. Therefore, susceptibility testing should be performed periodically during therapy to detect the emergence of bacterial resistance.

**Urinary Tract Infections:** Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, pyelonephritis, and pyelitis, caused by: *C. diversus, C. freundii, E. cloacae, E. coli, K. pneumoniae, K. oxytoca, M. morganii, P. mirabilis, P. aeruginosa, S. marcescens, S. aureus, S. epidermidis, S. faecalis*

**Skin and Soft Tissue Infections:** caused by: *E. cloacae, E. coli, K. pneumoniae, P. vulgaris, P. mirabilis, S. pyogenes, P. aeruginosa, S. aureus, S. epidermidis*

**Bone and Joint Infections:** caused by: *S. marcescens, P. aeruginosa, S. aureus, E. cloacae*

**Infectious Diarrhea:** (When antibacterial therapy is indicated) caused by: *E. coli (enterotoxigenic strains), C. jejuni, S. flexneri, S. sonnei*
Appropriate culture and susceptibility tests should be performed prior to initiating treatment in order to isolate and identify organisms causing the infection and to determine their susceptibilities to ciprofloxacin. Therapy with CIPRO® may be initiated before results of these tests are known. However, modification of this treatment may be required once results become available or if there is no clinical improvement. Culture and susceptibility testing performed periodically during therapy will provide information on the possible emergence of bacterial resistance. If anerobic organisms are suspected to be contributing to the infection, appropriate therapy should be administered.

## CONTRAINDICATIONS

CIPRO® (ciprofloxacin hydrochloride tablets) are contraindicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolone antibacterial agents.

## WARNINGS

**Children** The safety of CIPRO® (ciprofloxacin hydrochloride tablets) in children has not yet been established. Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies but not in weaned piglets (see TOXICOLOGY in Product Monograph). Histopathological examination of the weight-bearing joints in immature dogs revealed permanent lesions of the cartilage. Consequently, CIPRO® should not be used in prepubertal patients. Experience in pubertal patients below 18 years of age is limited.

**Pregnancy** The safety of CIPRO® in the treatment of infections in pregnant women has not yet been established (see PRECAUTIONS).

## PRECAUTIONS

**General** Anaphylactic reactions including cardiovascular collapse have occurred rarely in patients receiving therapy with CIPRO® (ciprofloxacin hydrochloride tablets). These reactions may occur within the first 30 minutes following the first dose and may require epinephrine and other emergency measures.

CIPRO® may cause central nervous system (CNS) stimulation which may lead to tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, CIPRO® should be used with caution in patients with CNS disorders, such as severe cerebral arteriosclerosis or epilepsy. Patients with known convulsive seizure disorders should only be treated with CIPRO® if anticonvulsant therapy has been initiated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been reported to occur very rarely in patients receiving ciprofloxacin in combination with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be withdrawn at the first appearance of a skin rash or other signs of hypersensitivity.

Crystalluria related to ciprofloxacin has been reported only rarely in man because human urine is usually acidic. Crystals have been observed in the urine of laboratory animals, usually from alkaline urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded.

Pseudomembranous colitis has been reported with virtually all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients with diarrhoea subsequent to the administration of antibacterial agents.

Subsequent to diagnosis of pseudomembranous colitis, therapeutic measures should be initiated. Mild cases will usually respond to discontinuation of drug alone. In moderate to severe cases, consideration should be given to the management with fluids, electrolytes, protein supplementation and treatment with an antibacterial drug effective against *C. difficile.*

Prolonged use of CIPRO® may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is therefore essential, and if superinfection should occur during therapy, appropriate measures should be taken.

**Pregnancy** The safety of CIPRO® in pregnancy has not yet been established. CIPRO® should not be used in pregnant women unless the likely benefits outweigh the possible risk to the fetus. CIPRO® has been shown to be non-embryotoxic and non-teratogenic in animal studies.

**Nursing Mothers** Ciprofloxacin is excreted in human milk. A decision should be made to discontinue nursing or to discontinue the administration of CIPRO®, taking into account the importance of the drug to the mother and the possible risk to the infant.

**Drug Interactions** Concurrent administration of ciprofloxacin with theophylline may lead to an elevated plasma concentration and prolongation of elimination half-life of theophylline. This may result in increased risk of theophylline-related adverse reactions.
If concomitant use cannot be avoided, plasma concentrations of theophylline should be monitored and dosage adjustments made as appropriate.

Ciprofloxacin has been shown to interfere with the metabolism and pharmacokinetics of caffeine. Excessive caffeine intake should be avoided.

Some quinolones, including ciprofloxacin, have been associated with transient increases in serum creatinine levels in patients who are concomitantly receiving cyclosporine.

Quinolones have been reported to increase the effects of the oral anticoagulant warfarin and its derivatives. During concomitant administration of these drugs, the prothrombin time or other appropriate coagulation tests should be closely monitored.

Probenecid blocks renal tubular secretion of ciprofloxacin and has been shown to produce an increase in the level of ciprofloxacin in the serum.

Concomitant administration of a nonsteroidal anti-inflammatory drug (fenbufen) with a quinolone (enoxacin) has been reported to increase the risk of CNS stimulation and convulsive seizures.

Antacids containing aluminum or magnesium hydroxide have been shown to reduce the absorption of ciprofloxacin. Concurrent administration with these agents should be avoided.

Administration of sucralfate prior to CIPRO® resulted in a 30% reduction in absorption of ciprofloxacin. Concurrent administration with ciprofloxacin should be avoided.

Oral ferrous sulfate at therapeutic doses decreases the bioavailability of oral ciprofloxacin, therefore concomitant therapy is not advised.

The use of calcium supplement reduces the absorption of ciprofloxacin. Concurrent administration should be avoided. In particular cases, concurrent administration of ciprofloxacin and glyburide can intensify the action of glyburide (hypoglycemia).

**Renal Impairment** Since ciprofloxacin is eliminated primarily by the kidney, CIPRO® should be used with caution and at a reduced dosage in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION).

**Hepatic Impairment** In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics were observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. An increased incidence of nausea, vomiting, headache and diarrhea were observed in this patient population.

## ADVERSE REACTIONS

CIPRO® (ciprofloxacin hydrochloride tablets) are generally well tolerated. During worldwide clinical investigation, 16,580 courses of ciprofloxacin treatment were evaluated for drug safety.

Adverse events, possibly, probably or highly probably related to ciprofloxacin occurred in 1395 (8.8%) of patients. The adverse reactions according to treatment (oral, iv, and sequential therapy) show that the incidence of adverse reactions was 8.0% for the group treated orally, 17% for the group treated with CIPRO® I.V. and 15.3% for the group treated sequentially. The difference between the oral and iv group relates to adverse vascular reactions which are known to be associated with iv administration.

In orally treated patients enroled in clinical trials, the most frequently reported events, possibly,probably drug-related were: nausea (1.3%) and diarrhea (1.0%).

Events possibly, probably drug-related occurring at a frequency of less than 1% with ciprofloxacin oral and i.v. treatment during clinical trials and subsequent post-marketing surveillance are as follows:

**Gastro-Intestinal:** vomiting, dyspepsia, abdominal pain, flatulence, dysphagia, enlarged abdomen, dry mouth, stomatitis, gastrointestinal moniliasis, anorexia, jaundice. The following have been reported very rarely: constipation, tooth discoloration, ulcerative stomatitis, pseudomembranous colitis, intestinal perforation, esophagitis, increased appetite, gastro-intestinal hemorrhage, melena, liver damage, tenesmus, ileus, toxic megacolon, hepatomegaly, glossitis.

**Cardiovascular System:** palpitation, tachycardia, phlebitis. The following have been reported very rarely: hypertension, hot flashes, cerebrovascular disorder, syncope, kidney vasculitis, vasodilation, atrial fibrillation, cardiac arrest, angina pectoris, electrocardiogram abnormality, myocardial infarct, substernal chest pain, pulmonary embolus, pericarditis, hypotension.

**Nervous System:** increased sweating, dizziness, agitation, tremor, somnolence, insomnia, confusion, hallucinations, convulsion, headache. The following have been reported very rarely: anxiety, depression, nervousness, apathy, depersonalization, abnormal dreams, hemiplegia, sleep disorder, neuritis, paresthesia, polyneuritis, diplopia, meningism, migraine, increase of intracranial pressure. In some instances these reactions occurred after the first administration of CIPRO® In these instances, CIPRO® has to be discontinued and the doctor should be informed immediately.

**Respiratory System:** dyspnea. The following have been reported very rarely: hiccup, increased cough, stridor, larynx edema, voice alteration, lung edema, pharyngitis, hyperventilation, lung hemorrhage.

**Skin and Appendages:** rash, pruritus. The following have been reported very rarely: urticaria, photosensitive dermatitis, angioedema, alopecia.

**Special Senses:** tinnitus, abnormal vision, taste perversion. The following have been reported very rarely: conjunctivitis, corneal opacity, eye pain, colour blindness, chromatopsia, diplopia, ear pain.

**Urogenital System:** albuminuria, hematuria. The following have been reported rarely: leukorrhea, dysuria, urinary retention, acute kidney failure, abnormal kidney function, nephritis, vaginitis.

**Hypersensitivity:** rash. The following have been reported rarely: pruritus, drug fever, anaphylactic/ anaphylactoid reactions including facial, vascular and laryngeal edema, serum sickness, petechiae, haemorrhagic bullae and small nodules (papules) with crust formation showing vascular involvement (vasculitis), Stevens-Johnson-syndrome, interstitial nephritis, hepatitis; very rarely, major liver disorders including hepatic necrosis, joint pain, Lyell Syndrome.

**Blood and Blood constituents:** eosinophilia, leukocytopenia, leukocytosis, anaemia, granulocytopenia. Very rarely: haemolytic anaemia, thrombocytopenia, thrombocytosis, altered prothrombin levels.

**Laboratory values:** increased alkaline phosphatase, Gamma - GT, transaminases, cholestatic parameters, lactic dehydrogenase, BUN, NPN, AST, ALT, decreased creatinine clearance, hypercholesteremia, albuminuria, bilirubinemia, hyperuricemia, increased sedimentation rate. The following have been reported rarely: electrolyte abnormality, hypercalcemia, hypocalcemia, acidosis, crystalluria and haematuria.

**Other:** thrombophlebitis. Very rarely, asthenia, death.

Most of the adverse events reported were described as only mild or moderate in severity.There have been 54 reports of arthropathies with CIPRO®. Ten of these reports involved children. Arthralgia was usually the first symptom which led to rapid assessment and withdrawal of the drug. No irreversible arthropathies have been observed.

## SYMPTOMS AND TREATMENT OF OVERDOSE

Overdose has not yet been reported with CIPRO® (ciprofloxacin hydrochloride tablets). In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment.

## DOSAGE AND ADMINISTRATION

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function.

### Oral Administration

CIPRO® (ciprofloxacin hydrochloride tablets) may be taken before or after meals. Absorption is faster on an empty stomach. Patients should be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

**Adult** The recommended dosages of oral CIPRO® are:

| Location of Infection | Type/Severity | Unit Dose | Frequency | Daily Dose |
|---|---|---|---|---|
| Urinary Tract | Mild/Moderate | 250 mg | q 12h | 500 mg |
| | Severe/Complicated | 500 mg | q 12h | 1000 mg |
| Lower Respiratory Tract | Mild/Moderate | 500 mg | q 12h | 1000 mg |
| Bone & Joint | Severe/Complicated* | 750 mg | q 12h | 1500 mg |
| Skin & Soft Tissue | | | | |
| Infectious Diarrhea | Mild/Moderate/Severe | 500 mg | q 12h | 1000 mg |

* e.g. hospital-acquired pneumonia, osteomyelitis

Depending on the severity of the infections, as well as the clinical and bacteriological responses, the average treatment period should be approximately 7 to 14 days. Generally, treatment should last 3 days beyond the disappearance of clinical symptoms or until cultures are sterile. Patients with osteomyelitis may require treatment for a minimum of 6 to 8 weeks and up to 3 months. With acute cystitis, a five-day treatment may be sufficient.

### Sequential IV/PO Therapy

In patients receiving intravenous ciprofloxacin, oral ciprofloxacin may be substituted when clinically indicated at the discretion of the physician. Clinical studies evaluating the use of sequential IV/PO therapy in septicemia have not yet been completed.

### Impaired Renal Function

Ciprofloxacin is eliminated primarily by renal excretion. However, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. This alternate pathway of drug elimination appears to compensate for the reduced renal excretion of patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides a guideline for dosage adjustment. However, monitoring of serum drug levels provides the most reliable basis for dosage adjustments. Only a small amount of ciprofloxacin (<10%) is removed from the body after haemodialysis or peritoneal dialysis.

| Creatinine Clearance mL/s (mL/min) | Dose |
|---|---|
| ≥ 0.5 (30) | No Dose adjustment |
| < 0.5 (30) and patients on haemodialysis or peritoneal dialysis | Use recommended dose once daily or half usual dose twice daily |

When only the serum creatinine concentration is available, the following formula (based on sex, weight and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function:

| | Creatinine Clearance mL/sec | | In traditional units mL/min |
|---|---|---|---|
| **Males:** | Weight (kg) x (140 - age) / 49 x serum creatinine (µmol/L) | **Males:** | Weight (kg) x (140 - age) / 72 x serum creatinine mg/100 mL |
| **Females:** | 0.85 x the above value | **Females:** | 0.85 x the above value |

### Children

The safety and efficacy of CIPRO® in children has not been established. CIPRO® should not be used in prepubertal patients (see WARNINGS).

## AVAILABILITY OF DOSAGE FORMS

**Tablets:**

**Cipro® 250** Each tablet is engraved CIPRO on one side and 250 on the other and contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin. Bottles of 100.

**Cipro® 500** Each tablet is engraved CIPRO on one side and 500 on the other and contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin. Bottles of 100 and unit dose packages of 100.

**Cipro® 750** Each tablet is engraved CIPRO on one side and 750 on the other and contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin. Bottles of 50 and unit dose packages of 100.

**Product Monograph available upon request.**



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Cipro®
ciprofloxacin hydrochloride

# Pr Dovonex®

▼ calcipotriol

## *Long-term control without steroid risks.*

***PRESCRIBING INFORMATION***

***PRODUCT NAME***

Pr DOVONEX ®
(Calcipotriol)

Ointment 50 µg/g

***THERAPEUTIC CLASSIFICATION***

Topical Non-Steroidal Antipsoriatic Agent

***ACTION AND CLINICAL PHARMACOLOGY***

Calcipotriol is a non-steroidal antipsoriatic agent, derived from the naturally occurring vitamin D. Calcipotriol exhibits a vitamin D-like effect by competing for the $1,25(OH)_2D_3$ receptor. Calcipotriol is as potent as $1,25(OH)_2D_3$ , the naturally occurring active form of vitamin D, in regulating cell proliferation and cell differentiation, but much less active than $1,25(OH)_2D_3$ in its effect on calcium metabolism. Calcipotriol induces differentiation and suppresses proliferation (without any evidence of a cytotoxic effect) of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis. The therapeutic goal envisaged with calcipotriol is thus a normalization of epidermal growth.

Calcipotriol formulated in an ointment vehicle was found to be efficacious and well-tolerated in the treatment of psoriasis vulgaris. Calcipotriol was used for the treatment of 686 patients with plaque-type psoriasis vulgaris participating in 5 clinical trials lasting from 6 to 8 weeks. The majority of patients had a marked improvement at the end of the treatment. Thickness, erythema and scaling were markedly improved. Only about 1% of the patients were withdrawn because of insufficient therapeutic response. It is characteristic that the improvement occurs rapidly. This data has been repeated in three long-term trials involving 334 patients with plaque-type psoriasis vulgaris treated for up to 12 months with calcipotriol ointment 50 µg/g. Combination of calcipotriol ointment with UVB phototherapy improved the therapeutic response, although to a statistically insignificant degree.

A pharmacokinetic study in psoriatic patients has demonstrated less than 1% systemic absorption of the applied dose of calcipotriol over 8 hours.

***INDICATIONS AND CLINICAL USES***

Calcipotriol ointment is indicated for the topical treatment of mild to moderate psoriasis.

***CONTRAINDICATIONS***

Hypersensitivity to any constituent of calcipotriol ointment. NOT FOR OPHTHALMIC USE.

***WARNINGS***

Calcipotriol ointment is not generally recommended for severe extensive psoriasis, in view of the risk of hypercalcemia secondary to excessive absorption of calcipotriol when there is extensive skin involvement. If calcipotriol is used for severe extensive psoriasis it is important to monitor the serum calcium levels at regular intervals. If the serum calcium level becomes elevated in such patients, calcipotriol therapy should be discontinued and the serum calcium level monitored in these patients until it returns to normal.

Calcipotriol ointment is not recommended for use on the face since this ointment may give rise to itching and erythema of the facial skin. Patients should be instructed to wash their hands after using calcipotriol ointment to avoid inadvertent transfer of this ointment to the face from other body parts. Should facial dermatitis develop in spite of these precautions, calcipotriol therapy should be discontinued (See Patient Package Insert).

*Use During Pregnancy and Lactation:* Safety for use during pregnancy has not yet been established, although studies in experimental animals have not shown teratogenic effects. It is not known whether calcipotriol could be excreted in breast milk. Calcipotriol should be used in women during pregnancy or breast feeding only if the anticipated benefit clearly outweighs the potential risk.

*Children:* There is inadequate experience with the use of calcipotriol ointment in children at present to recommend its use in this age group. Calcipotriol should be used in children only if the anticipated benefit clearly outweighs the potential risk.

***PRECAUTIONS***

Calcipotriol ointment should be used cautiously in skin folds, where the natural occlusion may give rise to an increase of the irritant effect of calcipotriol.

Treatment with calcipotriol ointment in the recommended amounts up to 100 g/week does not generally result in changes in laboratory values. However, it is recommended that base line serum calcium levels be obtained in all patients before starting treatment with calcipotriol ointment, with subsequent monitoring of these serum calcium levels at suitable intervals. The monitoring of serum calcium levels is particularly important if calcipotriol ointment is applied in excess of 100g/week or if calcipotriol ointment is used for severe psoriasis with extensive skin involvement. If the serum calcium becomes elevated, calcipotriol treatment should be discontinued, and the levels of serum calcium should be measured once weekly until the serum calcium levels return to normal values. Patients with marginally elevated serum calcium may be treated with calcipotriol, provided that the serum calcium is monitored at suitable intervals.

*Drug Interactions:* There is no experience of concomitant therapy with other antipsoriatic drugs applied to the same skin area.

***ADVERSE REACTIONS***

In clinical trials reported to-date, the most common adverse reactions have been related to lesional and perilesional irritation. Some patients develop face and scalp irritation which is likely related to the inadvertent transfer of the ointment from other body parts. One unconfirmed case of Koebner phenomenon has been reported and three unconfirmed cases of hypersensitivity reaction to calcipotriol. Occasionally hypercalcemia has been reported usually related to excessive (greater than

100 g/week) use of the ointment or when excessive absorption of calcipotriol ointment has occurred when used for severe psoriasis with extensive skin involvement (see Warnings).

***SYMPTOMS AND TREATMENT OF OVERDOSAGE***

Hypercalcemia does not occur at the usual dose of calcipotriol ointment (i.e., up to 100 g/week). Excessive use (ie.) more than 100 g/week may cause elevated serum calcium, which rapidly subsides when treatment is discontinued; in such cases the monitoring of serum calcium levels once weekly until the serum calcium returns to normal levels is recommended.

***DOSAGE AND ADMINISTRATION***

Calcipotriol ointment is available at a concentration of 50 µg/g. Calcipotriol ointment is indicated FOR TOPICAL USE ONLY and NOT FOR OPHTHALMIC USE.

*Adults:* Calcipotriol ointment should be applied topically to the affected area twice daily (i.e., in the morning and in the evening). Less frequent application may be indicated for maintenance treatment. After satisfactory improvement has occurred, the drug can be discontinued. If recurrence takes place after discontinuation, the treatment may be reinstituted.

**The maximum recommended weekly dosage of calcipotriol is 100g/week.**

Treatment with calcipotriol ointment can be combined with UVB phototherapy. Treated patients are allowed to expose the skin to sunlight. In such cases, the calcipotriol ointment should be applied after the exposure to UV light.

***STABILITY AND STORAGE RECOMMENDATIONS:***

Store at room temperature (15°C to 25°C) .

For easy application: do not refrigerate (this is to prevent rubbing and pulling of delicate skin).

***AVAILABILITY OF DOSAGE FORMS***

Dosage Form: Ointment (faintly translucent white to yellowish ointment)

Strength: 50 mcg calcipotriol per gram of ointment

Recommended Route of Administration: for topical use only

Containers: available in 30g and 100g lacquered aluminium tubes (equipped with an aluminium membrane)

Recommendation for application: For easy application: do not refrigerate (this is to prevent rubbing and pulling of delicate skin) .

Product monograph available upon request.

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PAAB

NEW PREPULSID 20 mg TABLET

**PREPULSID* cisapride monohydrate**

**TABLETS AND ORAL SUSPENSION**

**ACTIONS**

PREPULSID (cisapride monohydrate) is a gastrokinetic drug whose activity is considered to be due to enhancement of the physiological release of acetylcholine at the myenteric plexus.

Cisapride increases esophageal peristaltic activity and lower esophageal sphincter tone, thereby decreasing reflux of gastric contents into the esophagus and improving esophageal clearance. Gastric and duodenal emptying are also enhanced by cisapride as a consequence of increased gastric and duodenal contractility and antroduodenal coordination. Cisapride decreases duodenogastric reflux. It also enhances intestinal propulsive activity and improves both small and large bowel transit.

Cisapride is free of dopamine receptor blocking properties. It lacks cholinomimetic effects and therefore does not increase basal or pentagastrin induced gastric acid secretion.

Following oral administration in man, cisapride is rapidly and completely absorbed. Peak plasma levels are attained within 1 or 2 hours. Plasma levels proportionally increase with oral doses from 5 to 20 mg. At steady-state, morning pre-dose plasma levels and evening peak levels fluctuate between 10-20 ng/mL and 30-60 ng/mL respectively for 5 mg cisapride t.i.d., and between 20-40 ng/mL and 50-100 ng/mL for 10 mg t.i.d. The elimination half-life is 10 hours. Pharmacokinetics and steady-state levels are unrelated to the duration of treatment.

Cisapride undergoes extensive first-pass metabolism in the liver and in the gut wall. The main metabolic pathways are oxidative N-dealkylation and aromatic hydroxylation. The excretion of cisapride occurs mainly as metabolites in approximately the same amounts in urine and in faeces. The excretion in maternal milk is limited.

Cisapride is extensively bound to plasma proteins (97.5%), mainly to albumin.

**INDICATIONS AND CLINICAL USE**

PREPULSID cisapride monohydrate is indicated in the symptomatic management of gastrointestinal motility disorders including: gastroesophageal reflux disease; gastroparesis, idiopathic or associated with diabetic neuropathy; and intestinal pseudo-obstruction.

PREPULSID is also indicated for the prophylaxis of gastroesophageal reflux disease.

**CONTRAINDICATIONS**

PREPULSID cisapride monohydrate is contraindicated in patients with known sensitivity or intolerance to the drug.

PREPULSID is contraindicated whenever gastrointestinal stimulation might be dangerous i.e., gastrointestinal hemorrhage, mechanical obstruction or perforation.

**WARNINGS**

Use in Pregnancy

The anticipated therapeutic benefits should be weighed against potential hazards before giving PREPULSID during pregnancy, especially during the first trimester.

Use in Lactation

Although the excretion of PREPULSID in human breast milk is minimal, it is advisable to discontinue breastfeeding while taking PREPULSID.

**PRECAUTIONS**

Before initiating therapy with PREPULSID, organic disease such as gastrointestinal hemorrhage, mechanical obstruction or perforation should be excluded by the physician.

Use in Patients with Hepatic or Renal Insufficiency

Because of the importance of the liver and kidneys in the metabolism and excretion of PREPULSID, dosage should initially be reduced in patients with hepatic or renal insufficiency. (See DOSAGE AND ADMINISTRATION.)

Use in the Elderly

Steady-state plasma levels of PREPULSID are generally higher than those of younger patients due to a moderate prolongation of the elimination half-life. Initial therapeutic doses are similar to those used in younger patients but afterwards this dose can be adjusted depending on the therapeutic effects or possible side effects.

Drug Interactions

Since PREPULSID accelerates gastric emptying, the absorption from the stomach of other concomitantly administered drugs may be diminished whereas absorption of drugs from the small bowel may be accelerated.

In the case of drugs that require careful individual titration, such as anticonvulsants, it may be useful to monitor the plasma levels of such drugs when cisapride is given concomitantly.

In patients receiving anticoagulants, the coagulation times may increase. It is advisable to check coagulation time one week after the initiation and termination of PREPULSID therapy, with appropriate adaptation of the anticoagulant dose, if necessary.

Although PREPULSID does not affect psychomotor function nor does it induce sedation or drowsiness when used alone, the sedative effects of benzodiazepines and of alcohol may be enhanced by PREPULSID.

The beneficial effects of PREPULSID on gastrointestinal motility are largely antagonized by anticholinergic drugs.

Concomitant treatment with cimetidine or ranitidine increases slightly the oral bioavailability of PREPULSID.

**ADVERSE REACTIONS**

The most frequent side effects encountered with PREPULSID are gastrointestinal in nature: diarrhea and abdominal discomfort. Most side effects are transient and rarely necessitate discontinuation of therapy.

| | |
|---|---|
| Gastrointestinal: | diarrhea (5.1%), abdominal pain/cramps (2.1%), nausea, abdominal distension, (9.9%)constipation, borborygmi, flatulence, increased appetite (all < 1.0%). There may be an increased incidence of abdominal cramps with 20 mg per intake. Should severe abdominal cramps occur it is recommended to halve the dose per intake. |
| Central Nervous System: (3.3%) | headache (1.6%), mental disorders, sedation, fatigue, sleep disorders (all < 0.5%). There are isolated reports of convulsive seizures and extrapyramidal effects without clearcut relationship to PREPULSID. |
| Dermatological: (0.9%) | rash, pruritus (each < 0.5%) |
| Cardiovascular: (0.6%) | orthostatic hypotension, palpitations, tachycardia, hot flushes (all < 0.2%) |
| Genitourinary: (0.5%) | mastalgia, menstrual disorder, pollakiuria, urinary incontinence (all < 0.1%) |
| Musculoskeletal: | back pain, heaviness in limbs (< 0.2%) (0.3%) |
| Miscellaneous: | Vertigo/dizziness (1.2%), blurred vision (0.2%) |

Exceptional cases of reversible liver function abnormalities, with or without cholestasis, have been reported. A causal relationship with PREPULSID has not been unequivocally established.

In addition, other side effects, such as edema (unspecified) and hemorrhoids have been observed during PREPULSID therapy. The relationship to the drug is unclear.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There has been only limited experience with overdosage of PREPULSID, however, the following signs and symptoms might be expected to occur: abdominal cramping, diarrhea, dizziness, faintness, hypotension. In infants, mild sedation, apathy and atony have also been observed.

In case of overdosage, the administration of activated charcoal and close observation of the patient are recommended.

**DOSAGE AND ADMINISTRATION**

**TABLETS AND ORAL SUSPENSION**

**Adults**

Gastroesophageal Reflux Disease

Symptomatic Management:

5 to 10 mg PREPULSID, three to four times daily, 15 minutes before meals and at bedtime; or 20 mg PREPULSID, twice daily, before breakfast and at bedtime.

Prophylaxis:

10 mg PREPULSID, twice daily, before breakfast and at bedtime; or 20 mg PREPULSID, once daily, at bedtime. In patients with severe disease, it may be necessary to increase the dose to a maximum of 20mg twice daily.

PREPULSID should be taken with a beverage.

Gastroparesis and Pseudoobstruction

The usual dose is 10 mg PREPULSID, three to four times daily, 15 minutes before meals and at bedtime.

PREPULSID should be taken with a beverage.

Although improvement will usually be obtained within the first weeks of treatment, maximal effect may not be seen until the patient has completed 8 to 12 weeks of continuous therapy.

Use in Patients with Hepatic and Renal Insufficiency

In patients with hepatic or renal insufficiency, the initial daily dose should be reduced. Afterwards the dose can be adjusted depending on therapeutic effect or possible side effects.

Use in the Elderly

Therapeutic doses in the elderly are similar to those used in younger adults; however, because of a moderate prolongation of the elimination half-life, the steady-state plasma levels tend to be higher. More careful titration to the lowest effective dose may be necessary.

**COMPOSITION**

Tablets: Each tablet contains either 5 mg, 10 mg, or 20 mg cisapride, as cisapride monohydrate.

Suspension: Each mL of white cherry cream flavoured suspension contains 1mg of cisapride, as cisapride monohydrate.

**STABILITY AND STORAGE RECOMMENDATIONS**

Storage: PREPULSID 5 mg tablets, 10 mg tablets, 20 mg tablets and 1 mg/mL suspension should be stored at room temperature and protected from moisture and light.

**AVAILABILITY OF DOSAGE FORMS**

Tablets: Each white to slightly beige, circular, biconvex half scored tablet is inscribed with $\frac{Cis}{5}$ (5 mg), $\frac{P}{10}$ (10 mg), or $\frac{Cis}{20}$ (20 mg) on the scored side, and JANSSEN on the other side. Tablets of 5 mg available in HDPE bottles of 100 and 500; tablets of 10 mg available in HDPE bottles of 500; tablets of 20 mg available in HDPE bottles of 250.

Oral Suspension: Amber glass bottles of 200 mL.

Cisapride is a Schedule F drug.

Product monograph is available to Health Professionals upon request.

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**Prepulsid***

CISAPRIDE

RELIEVING MORE THAN JUST PAIN BY RESTORING DIGESTIVE MOVEMENT.

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# Livostin®

(levocabastine HCl)

**PRESCRIBING INFORMATION**

# LIVOSTIN* Eye Drops

(Levocabastine hydrochloride ophthalmic suspension)
0.5mg levocabastine/mL

**THERAPEUTIC CLASSIFICATION** Histamine $H_1$-antagonist

**ACTION AND CLINICAL PHARMACOLOGY**

LIVOSTIN* (levocabastine hydrochloride) is a potent, fast-acting and highly selective histamine $H_1$-antagonist with a sustained duration of action.

Within 10-15 minutes of topical application to the eyes, levocabastine inhibits itching, redness and chemosis induced by conjunctival provocation with histamine; itching, redness, chemosis, eyelid swelling, and tearing induced by conjunctival provocation with allergens; and itching and redness induced by conjunctival provocation with compound 48/80.

Orally-administered levocabastine provides a dose dependent inhibition of skin reactions to intradermal histamine. After topical application to the eyes levocabastine did not produce clinically significant systemic antihistamine effects in patients.

Levocabastine eye drops (2 drops/eye t.i.d.), under acute and steady state conditions, are devoid of CNS effects, as evaluated by objective and subjective psychoperformance tests and measures of general CNS activity.

Following topical application to the eyes, the absorption of levocabastine was incomplete and the absolute bioavailability of levocabastine instilled in the eyes could be estimated at approximately 30% in patients with allergic conjunctivitis and up to 60% in healthy volunteers.

**INDICATIONS AND CLINICAL USE**

LIVOSTIN (levocabastine hydrochloride) eye drops are indicated for the symptomatic management of seasonal allergic conjunctivitis.

**CONTRAINDICATIONS**

LIVOSTIN (levocabastine hydrochloride) eye drops are contraindicated in patients with hypersensitivity to any of the ingredients.

**WARNINGS: Use in Children**

Levocabastine is not recommended for use in children under the age of 12 years except on the advice of a physician. Clinical experience in children under 5 years of age is limited with ocular levocabastine.

**PRECAUTIONS**

As with all ophthalmic preparations containing benzalkonium chloride, patients are advised not to wear soft (hydrophilic) contact lenses while under treatment with LIVOSTIN (levocabastine hydrochloride) eye drops.

**Use in Pregnancy and Lactation**

There are no clinical trials on the use of LIVOSTIN eye drops in pregnant or nursing women, therefore, LIVOSTIN eye drops should not be used during pregnancy, except if the potential benefit justifies the potential risk to the foetus.

**Use in Elderly**

The safety and efficacy of topical levocabastine has not been established in patients greater than 65 years of age.

**ADVERSE REACTIONS**

The most frequent side effect encountered with LIVOSTIN (levocabastine hydrochloride) eye drops is eye irritation. Most side effects are transient and rarely necessitate discontinuation of therapy. See Table 1.

Table 1: Incidence of the most frequent+ adverse experiences in patients treated with LIVOSTIN eye drops or placebo eye drops.

| | INCIDENCE (%) | |
|---|---|---|
| **ORGAN SYSTEM** | **LIVOSTIN** Eye Drops (n=599) | **PLACEBO** Eye Drops (n=215) |
| **Ocular** | **19.9** | **18.6** |
| eye irritation | 16.4 | 15.8 |
| dry conjunctiva | <1.0 | 0.0 |
| The others (blurred vision, eye discharge, eyelid oedema, eye pain and abnormal lacrimation) were <1.0% for both the LIVOSTIN and PLACEBO groups. | | |
| **Central Nervous System** | **6.0** | **9.3** |
| headache | 3.5 | 4.2 |
| somnolence | 2.0 | 5.1 |
| insomnia | <1.0 | 0.0 |
| **Respiratory System** | **4.2** | **5.1** |
| coughing | 1.0 | 1.4 |
| epistaxis | 1.0 | <1.0 |
| nasal congestion | <1.0 | 0.0 |
| rhinorrhoea | <1.0 | 1.4 |
| The others (nasal irritation, itchy throat, pharyngitis and dyspnoea) were <1.0% for both the LIVOSTIN and PLACEBO groups. | | |
| tiredness | 2.0 | 1.4 |
| dry mouth | 1.0 | 4.2 |
| fever | <1.0 | 0.0 |
| rash | <1.0 | 0.0 |
| generalized pruritus | <1.0 | <1.0 |
| pruritus | <1.0 | 0.0 |
| nausea | <1.0 | 0.0 |

+Reported more than once in the LIVOSTIN group.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There has been no experience with overdosage of LIVOSTIN (levocabastine hydrochloride) eye drops. Treatment should include general supportive measures.

**DOSAGE AND ADMINISTRATION**

Adults and children (12 to 65 years old): the usual dose is 1 drop (15 µg) of LIVOSTIN eye drops instilled in each eye, 2 times daily. The dose may be increased to 1 drop 3 to 4 times daily.

It is not useful to continue the treatment for more than 3 days if no improvement is seen. There are no clinical studies to support continuous treatment durations of greater than 16 weeks.

As LIVOSTIN eye drops are available as a microsuspension, the bottle should be shaken before each application. LIVOSTIN eye drops should be used within one month of the first opening of the bottle. Patients should be instructed to take appropriate measures to avoid contamination.

**PHARMACEUTICAL INFORMATION**

**Drug Substance**

| | |
|---|---|
| Trade Name: | LIVOSTIN* |
| Proper Name: | levocabastine hydrochloride |
| Chemical Name: | (-)-[3s-[1(cis),3∝,4ß]]-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidine-carboxylic acid monohydrochloride |
| Molecular Formula: | $C_{26}H_{29}FN_2O_2$•HCl |
| Molecular Weight: | 456.99 |

Description: Levocabastine hydrochloride is a white to almost white powder with a melting temperature of > 300°C, a $pKa_1$ of 3.1 and a $pKa_2$ of 9.7. It is freely soluble in dimethylsulfoxide; soluble in N,N-dimethylformamide and methanol; slightly soluble in propylene glycol, polyethylene glycol and ethanol; in aqueous medium the solubility is a function of pH, with minimum solubility at pH 4.1 to 9.8. The log-partition coefficient (n-octanol/aqueous buffer at pH 8.0) is 1.82.

**Composition**

LIVOSTIN eye drops are available as a sterile ophthalmic microsuspension (pH 6-8). Each mL contains levocabastine hydrochloride (equivalent to 0.5mg levocabastine) as active ingredient; benzalkonium chloride 0.15mg as preservative; and propylene glycol, polysorbate80, disodium phosphate, monosodium phosphate, disodium edetate, hypromellose and water as inactive excipients.

**Stability and Storage Recommendations:**

LIVOSTIN should be stored between 15 and 25 °C.

**AVAILABILITY OF DOSAGE FORM**

*LIVOSTIN (levocabastine hydrochloride) eye drops are available in 5 mL plastic bottles containing 4mL of white microsuspension.

# LIVOSTIN* Nasal Spray

(Levocabastine hydrochloride suspension)
0.5 mg levocabastine/mL

**THERAPEUTIC CLASSIFICATION**

Histamine $H_1$-antagonist

**ACTION AND CLINICAL PHARMACOLOGY**

LIVOSTIN* (levocabastine hydrochloride) is a potent, fast-acting and highly selective histamine $H_1$-antagonist with a sustained duration of action.

Within 10 minutes of topical application to the nose, levocabastine inhibits sneezing, itchy nose and rhinorrhoea induced by nasal provocation with allergens.

Orally administered levocabastine provides a dose dependent inhibition of skin reactions to intradermal histamine. After repeated topical application to the nose, topical and systemic antihistamine effects contribute to overall clinical outcome. Although systemic effects may contribute to the therapeutic effects of levocabastine nasal spray, this is not accompanied by any sedative effects.

Levocabastine nasal spray (2 sprays/nostril t.i.d.), under acute and steady state conditions, is devoid of CNS effects, as evaluated by objective and subjective psychoperformance tests and measures of general CNS activity.

Following topical application to the nose, the absorption of levocabastine was incomplete and the absolute bioavailability of levocabastine administered in the nose could be estimated at 60-80% in healthy volunteers and in patients with allergic rhinitis.

**INDICATIONS AND CLINICAL USE**

LIVOSTIN (levocabastine hydrochloride) nasal spray is indicated for the symptomatic treatment of allergic rhinitis (sneezing, itchy nose, runny nose).

**CONTRAINDICATIONS**

LIVOSTIN (levocabastine hydrochloride) nasal spray is contraindicated in patients with hypersensitivity to any of the ingredients.

**WARNINGS**

**Use in Pregnancy and Lactation**

There are no clinical trials on the use of LIVOSTIN nasal spray in pregnant or nursing women, therefore, LIVOSTIN (levocabastine hydrochloride) nasal spray should not be used during pregnancy, except if the potential benefit justifies the potential risk to the foetus.

**Use in Children**

Levocabastine is not recommended for use in children under the age of 12 years except on the advice of a physician. Clinical experience in children under 5 years of age is absent with nasal levocabastine.

**PRECAUTIONS**

Since levocabastine is excreted renally, caution should be exercised when administering LIVOSTIN (levocabastine hydrochloride) nasal spray to patients with renal impairment.

**Use in Elderly**

The safety and efficacy of topical levocabastine has not been established in patients greater than 65 years of age.

**Drug Interactions**

Interaction with alcohol or any other drug was never reported in clinical trials. In a specially designed psychoperformance study, an interaction with diazepam was not observed but a slight interaction with alcohol could not be excluded.

**ADVERSE REACTIONS**

The most frequent side effect encountered with LIVOSTIN (levocabastine hydrochloride) nasal spray is nasal irritation. Most side effects are transient and rarely necessitate discontinuation of therapy. See Table 1.

Table 1: Incidence of the most frequent+ adverse experiences in patients treated with LIVOSTIN nasal spray or placebo nasal spray.

| | INCIDENCE (%) | |
|---|---|---|
| **ORGAN SYSTEM** | **LIVOSTIN** Nasal Spray (n=702) | **PLACEBO** Nasal Spray (n=427) |
| **Respiratory System** | **10.4** | **9.6** |
| nasal irritation | 5.4 | 5.6 |
| epistaxis | 1.0 | <1.0 |
| Coughing, throat irritation, respiratory disorder, aggravated nasal obstruction and nasal pruritus were <1.0% in the LIVOSTIN group and not reported in the PLACEBO group. The others (dry nose, rhinorrhoea, dyspnoea, itchy throat) were <1.0% for both the LIVOSTIN and PLACEBO groups. | | |
| **Central Nervous System** | **7.7** | **7.0** |
| somnolence | 3.8 | 3.5 |
| headache | 3.1 | 3.0 |
| dizziness | <1.0 | <1.0 |
| **Ocular** | **3.0** | **2.1** |
| eye irritation++ | 2.6 | 1.9 |
| **Other** | | |
| dry mouth | 3.3 | 2.6 |
| tiredness | 1.4 | 1.0 |
| Facial oedema, rash, decreased hearing, pruritus of external ear and taste perversion were <1.0% in the LIVOSTIN group and not reported in the PLACEBO group. The others (abdominal pain, increased appetite, nausea and increased weight) were <1.0% for both the LIVOSTIN and PLACEBO groups. | | |

+ Reported more than once in the LIVOSTIN group.

++ The eye irritation observed in the levocabastine nasal spray group was mostly reported by the patients receiving both the levocabastine nasal spray and eye drops.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There has been no experience with overdosage of LIVOSTIN (levocabastine hydrochloride) nasal spray. Treatment should include general supportive measures.

**DOSAGE AND ADMINISTRATION**

Adults and children (12 to 65 years old): the usual dose is 2 sprays (50 µg/spray) of LIVOSTIN (levocabastine hydrochloride) nasal spray per nostril, 2 times daily. The dose may be increased to 2 sprays 3 to 4 times daily.

It is not useful to continue the treatment for more than 3 days if no improvement is seen. There are no clinical studies to support continuous treatment durations of greater than 10 weeks.

As LIVOSTIN nasal spray is available as a microsuspension, the bottle should be shaken before each application. Patients should be instructed to clear the nasal passages prior to administering the spray and to inhale through the nose during spraying. Before using the pump delivery system for the first time, the pump reservoir should be filled up by priming until a fine spray is delivered.

**PHARMACEUTICAL INFORMATION**

**Drug Substance**

| | |
|---|---|
| Trade Name: | LIVOSTIN* |
| Proper Name: | levocabastine hydrochloride |
| Chemical Name: | (-)-[3s-[1(cis),3∝,4ß]]-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidine-carboxylic acid monohydrochloride |
| Molecular Formula: | $C_{26}H_{29}FN_2O_2$•HCl |
| Molecular Weight: | 456.99 |

Description: Levocabastine hydrochloride is a white to almost white powder with a melting temperature of > 300°C, a $pKa_1$ of 3.1 and a $pKa_2$ of 9.7. It is freely soluble in dimethylsulfoxide; soluble in N,N-dimethylformamide and methanol; slightly soluble in propylene glycol, polyethylene glycol andethanol; in aqueous medium the solubility is a function of pH, with minimum solubility at pH 4.1 to 9.8. The log-partition coefficient (n-octanol/aqueous buffer at pH 8.0) is 1.82.

**Composition**

LIVOSTIN nasal spray is available as a microsuspension (pH 6-8). Each ml contains levocabastine hydrochloride (equivalent to 0.5 mg levocabastine) as active ingredient; benzalkonium chloride 0.15 mg as preservative; and propylene glycol, polysorbate80, disodium phosphate, monosodium phosphate, disodium edetate, hypromellose and water as inactive excipients.

**Stability and Storage Recommendations**

LIVOSTIN should be stored at room temperature (15-30°C).

**AVAILABILITY OF DOSAGE FORM**

*LIVOSTIN* (levocabastine hydrochloride) nasal spray is available in 15 mL plastic bottles containing 10mL of white microsuspension.

**References: 1.** Søhoel P, Freng BA, Kramer J et al. Topical levocabastine compared with orally administered terfenadine for the prophylaxis and treatment of seasonal rhinoconjunctivitis. J Allergy Clin Immunol 1993;92:73-81. **2.** Janssens MM-L, Vanden Bussche G. Levocabastine: an effective topical treatment of allergic rhinoconjunctivitis. Clin Exp Allergy 1991;21(Suppl 2):29-36. **3.** Davies RJ, Weeks B. Introductory comments. Clin Exp Allergy 1991;21(Suppl 2):1. **4.** Tomiyama S, Ohnishi M, Okunda M. The dose and duration of effect of levocabastine, a new topical $H_1$ antagonist, on nasal provocation reaction to allergen. Am J Rhinology 1993;7(2):85-88. **5.** Azevedo M, Castel-Branco MG, Ferraz Oliveira J et al. Double-blind comparison of levocabastine eye drops with sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis. Clin Exp Allergy 1991;21:689-94. **6.** Abelson MB, George MA, Smith LM. Evaluation of 0.05% levocabastine versus 4% sodium cromolyn in the allergen challenge model. Paper presented at the Academy of Ophthalmology Annual Meeting, Anaheim, CA, October 13-18, 1991. **7.** Livostin product monograph.

# Tilade®

NEDOCROMIL SODIUM

NON-STEROID ANTI-INFLAMMATORY

Nedocromil Sodium Inhalation Aerosol
2mg/metered dose

**THERAPEUTIC CLASSIFICATION**
Bronchial Anti-inflammatory Agent

**ACTIONS AND CLINICAL PHARMACOLOGY**
TILADE (nedocromil sodium) is a new chemical entity that inhibits the release of inflammatory mediators from a variety of cell types occurring in the lumen and in the mucosa of the bronchial tree. When it is administered topically to the bronchi, it displays specific anti-inflammatory properties. Laboratory experiments have shown that nedocromil sodium prevents the release of inflammatory chemotactic and smooth muscle contracting mediators, which are preformed or derived from arachidonic acid metabolism by both the lipoxygenase and cyclo-oxygenase pathways, in a range of human and animal leucocytes. Nedocromil sodium prevents the release of mediators such as histamine, Leukotriene $C_4$ ($LTC_4$) and Prostaglandin $D_2$ ($PGD_2$) from the cellular population of the chronically inflamed bronchus, especially from mast cells of the mucosal type. There is growing evidence that these mediators are important in human lung disease, and TILADE may, therefore, be expected to have more scope in the management of chronic reversible obstructive airways disease in which allergy, inflammation and bronchial hyper-responsiveness are significant pathophysiological factors.

After inhalation, TILADE is deposited throughout the respiratory tract where about 5% of the dose is absorbed. Because TILADE is inhaled much of the delivered dose is either swallowed directly or subsequently due to mucociliary clearance from the large airways. A small amount of nedocromil sodium (2 to 3%) is then absorbed from the gastrointestinal tract. Since the absorption rate constant from the respiratory tract is lower than the elimination rate constant in bile and urine, the terminal half-life (1.5 to 2 hours) reflects the absorption rate of the lungs. The drug is cleared rapidly enough from the circulation such that successive doses in the recommended dosing regimen do not accumulate.

Nedocromil sodium is bound reversibly (80%) to human plasma proteins and to a lesser extent in animals. It is not metabolized in man or in animals. In man it is excreted unchanged in the urine (approximately 70%) and in faeces (approximately 30%). While the plasma concentration falls rapidly (i.e., to 10% of peak levels in 8 hours) and urinary excretion is 90% complete within 12 hours, faecal elimination may take up to 3 days to be completed.

The pharmacokinetic profile of nedocromil sodium is similar in healthy volunteers and in patients with reversible obstructive airways disease. In challenge studies, a single dose of TILADE provided protection against bronchospasm provoked by stimulants such as, inhaled allergens, cold air, exercise and atmospheric pollutants.

**INDICATIONS AND CLINICAL USE**
TILADE (nedocromil sodium) is indicated as an adjunctive in the treatment of mild to moderate reversible obstructive airways disease, including bronchial asthma and bronchitis, particularly where allergic factors may be present.

TILADE can also be used on a maintenance or on an occasional basis in the prevention of bronchospasm provoked by stimulants, such as, inhaled allergens, cold air, exercise and atmospheric pollutants.

TILADE may be used safely with other anti-asthma drugs. The addition of TILADE may permit reduction of concomitant therapy.

**CONTRAINDICATIONS**
Known hypersensitivity to TILADE (nedocromil sodium), to sorbitan trioleate or to propellants such as dichlorotetrafluorethane and dichlorodifluoromethane.

**WARNINGS**
TILADE (nedocromil sodium) should not be used for the relief of an acute attack of bronchospasm.

**PRECAUTIONS**
IN THE TREATMENT OF ASTHMA, TILADE (nedocromil sodium) SHOULD NOT BE USED AS AN ALTERNATIVE TO BRONCHODILATORS. However, addition of TILADE to the treatment regimen can reduce the need for concomitant medications. **This reduction should be done slowly and under close supervision. The requirements for the reduction of corticosteroids have not been established.**

To ensure optimal delivery to the bronchial tree patients should be carefully instructed in the proper use of the inhaler. For maximum benefit, patients should be reminded of the necessity to take TILADE regularly, as prescribed.

Abuse of fluorocarbon propellants may be hazardous. Deliberate inhalation of propellants in high concentrations, particularly under conditions of hypoxia, has resulted in toxic cardiovascular effects, severe CNS disturbances and death. Acute toxic effects of TILADE would be restricted to pronounced overdose or to aerosol induced bronchoconstriction. Nedocromil sodium itself has an extremely low acute toxicity.

**Use in Pregnancy** Safety in human pregnancy and the absence of adverse effects on the human reproductive process have not been established. Small amounts are known to cross the placenta but without effect in animals. In fact, in reproductive studies, nedocromil sodium at up to 100mg/kg (more than 800 times the human maintenance dose) has shown no teratogenic or embryotoxic effects, nor has it interfered with reproductive performance, gestation, parturition, or suckling. Nedocromil sodium did not affect male or female fertility nor did it alter the development of progeny.

Although there is no reason to suspect that nedocromil sodium affects the fetus or mother, as with any drug, caution must be exercised. The benefits of treatment to the mother must be weighed against the potential risk to the fetus before proposing its use.

**Nursing Mothers** Safety in breast-fed infants has not been established. Animal studies have indicated no toxicity of nedocromil sodium in suckling newborns receiving drug from the parent or directly by injection. The concentrations of nedocromil sodium in milk of animals were very low but have not been measured in human milk.

The benefits of treating a nursing mother must be weighed against potential risk to the infant.

**Use in Children** The safety and efficacy of TILADE in children under twelve years of age has not yet been established.

**Drug Interactions** TILADE has been used in association with other antiasthmatic drugs in man including $\beta_2$-adrenergic agonists, inhaled and oral corticosteroids, theophylline and other methylxanthines and, with ipratropium bromide. No drug-drug interactions have been observed in humans or in animals.

**ADVERSE REACTIONS**
Few side effects have been reported, principally unpleasant taste, headache and nausea, that have been mild and transient and insufficient to require discontinuation of treatment in nearly all cases.

Specific side effects and their frequencies of occurrence with chronic dosing are unpleasant taste 13.4%, headache 4.8%, nausea 3.8% and vomiting 1.1%.

**SYMPTOMS AND TREATMENT OF OVERDOSE**
There have been no reported cases of overdosage in humans. Animal studies have not shown evidence of toxic effects of TILADE (nedocromil sodium), even at high dosage. If overdosage is suspected, treatment should be supportive and directed to the control of the relevant symptoms.

**DOSAGE AND ADMINISTRATION**
TILADE (nedocromil sodium) is intended for regular daily usage and should not be used for relief of symptoms during an acute attack.

The therapeutic benefits of repeated doses of TILADE will be apparent in most patients within one week of starting treatment, but it may take longer on occasion.

**Adults and children over 12 years of age:** In initial and maintenance therapy, two actuations (4mg of nedocromil sodium) four times daily. Some patients can be maintained with two actuations twice daily.

TILADE in a single dose of two actuations (4mg) a few minutes before exposure provides protection against bronchospasm provoked by stimulants, such as, inhaled allergens, cold air, exercise and atmospheric pollutants.

**DOSAGE FORM**
Each 17mL pressurized, aluminum canister contains nedocromil sodium and sorbitan trioleate as surfactant with dichlorotetrafluorethane and dichlorodifluoromethane as propellants. Units are filled with material to provide a minimum of 112 metered actuations, delivering 2mg of nedocromil sodium. The pack consists of an aerosol canister with a plastic adapter and a patient instruction sheet.

*Product monograph available upon request.*

**References:**


1. Bergmann KCh, et al. Curr Med Res Opin 1989;**11**(8):533-42.
2. Bel EH, et al. Am Rev Respir Dis 1990;**141**:21-28.
3. Cherniak RM, et al. Chest 1990;**97**: 1299-1306.
4. Wasserman S. J Allergy Clin Immunol 1993;**92**(1:2)210-215.
5. Tilade Product Monograph.
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7. Crimi E, Brusaco V, Crimi P. J Aller Clin Immunol 1989;**83**(5):985-990.



FISONS
Pharmaceuticals
Fisons Corporation Limited
1851 Sandstone Manor
Pickering, Ontario
L1W 3R9

# PROZAC®

## As your first line of action.

**Brief summary. Consult the Product Monograph for complete prescribing information.**

**INDICATIONS** — PROZAC (fluoxetine) may be indicated for the symptomatic relief of depressive illness.

**CONTRAINDICATIONS** — PROZAC (fluoxetine) is contraindicated in patients with known hypersensitivity to the drug. *Monoamine Oxidase Inhibitors* – There have been reports of serious, sometimes fatal, reactions in patients receiving PROZAC in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued PROZAC and then started on an MAOI. PROZAC should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping PROZAC before starting an MAOI.

**WARNINGS — Allergic Reactions** (Rash and Accompanying Events): Of 5,600 patients given fluoxetine approximately 4% developed a rash and/or urticaria. Almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Reported in association with these allergic reactions include rash, fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely. Two patients are known to have developed a serious cutaneous systemic illness. One was considered to have a leukocytoclastic vasculitis, and the other severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations suggestive of serum sickness. Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events. Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported. Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom. Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, PROZAC should be discontinued. **Implications of the Long Elimination Half-Life of Fluoxetine:** Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment.

**PRECAUTIONS** — Nervousness and insomnia were reported by 10 to 15% of patients treated with PROZAC (fluoxetine). These symptoms led to discontinuation of the drug in 5% of the patients. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with PROZAC. Hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence of seizures associated with fluoxetine during clinical trials did not appear to differ from that reported with other marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials. The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. High risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. Prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management. PROZAC should be used cautiously in patients, especially those with diseases or conditions that could affect metabolism or hemodynamic responses. PROZAC has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Retrospective evaluation of EKGs in these studies showed no conduction abnormalities that resulted in heart block. The mean heart rate was reduced by approximately 3 beats/minute. In patients with diabetes, fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued. Patients should be cautioned against driving an automobile or performing hazardous tasks until they are reasonably certain that treatment with PROZAC does not affect them adversely. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients. Cases of hyponatremia have been reported. The hyponatremia appeared to be reversible when PROZAC was discontinued. Some cases were possibly due to SIADH. The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role. **Use in Pregnancy and Lactation:** Safe use of fluoxetine during pregnancy and lactation has not been established. Therefore it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus. **Use in Children:** Safety and effectiveness in patients below the age of 18 have not been established. **Use in the Elderly:** Elderly patients should initially receive fluoxetine in low dosage with slow progressive increases only if required and tolerated. Patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly should be under careful observation at all dosage levels.

**DRUG INTERACTIONS** — There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when PROZAC has been administered in combination with these agents. Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress. There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly. Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (eg, warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

**ADVERSE REACTIONS** — The most commonly observed adverse events associated with the use of PROZAC (fluoxetine) and not seen at an equivalent incidence among placebo treated patients were: central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or lightheadedness; gastrointestinal complaints, including nausea, diarrhea, dry mouth and anorexia; and excessive sweating. Fifteen percent of approximately 4,000 patients who received PROZAC in North American clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (2.4%), primarily dizziness, asthenia, and headaches; skin (1.4%), primarily rash and pruritus. Suicidal thoughts and acts are far more common among depressed patients than in the general population. It is estimated that suicide is 22 to 36 times more prevalent in depressed persons than in the general population. A comprehensive meta-analysis of pooled data from 17 double-blind clinical trials in patients with major depressive disorder compared fluoxetine (n=1765) with a tricyclic antidepressant (n=731) or placebo (n=569), or both. The pooled incidence of emergence of substantial suicidal ideation was 1.2% for fluoxetine, 2.6% for placebo, and 3.6% for tricyclic antidepressants. The following adverse reactions, arranged by body system, were reported on at least one occasion by patients during treatment with PROZAC either during clinical trials or after marketing. **Allergic or Toxic:** rash, pruritus. Infrequent: chills and fever, urticaria, maculopapular rash. Rare: allergic reaction, erythema multiforme, vesiculobullous rash, serum sickness, contact dermatitis, erythema nodosum, purpuric rash, leukocytoclastic vasculitis, leukopenia, thrombocytopenia, arthralgia, angioedema, bronchospasm, lung fibrosis, allergic alveolitis, larynx edema, respiratory distress. **Neurologic:** headache, tremor, dizziness or lightheadedness, asthenia. Infrequent: abnormal gait, ataxia, akathisia, buccoglossal syndrome, hyperkinesia, hypertonia, incoordination, neck rigidity, extrapyramidal syndrome, convulsions, photophobia, myoclonus, vertigo, migraine, tinnitus, hypesthesia, neuralgia, neuropathy, acute brain syndrome. Rare: dysarthria, dystonia, torticollis, decreased reflexes, nystagmus, paralysis, paresthesia, carpal tunnel syndrome, stupor, coma, abnormal electroencephalogram, chronic brain syndrome, dyskinesia and other movement disorders (including worsening of preexisting conditions or appearance in patients with risk factors [eg, Parkinson's disease, treatment with neuroleptics or other drugs known to be associated with movement disorders]), neuroleptic malignant syndrome-like events. **Behavioural:** insomnia, anxiety, nervousness, agitation, abnormal dreams, drowsiness and fatigue. Infrequent: confusion, delusions, hallucinations, manic reaction, paranoid reaction, psychosis, depersonalization, apathy, emotional lability, euphoria, hostility, amnesia, increased libido. Rare: antisocial reaction, hysteria, suicidal ideation, violent behaviours. **Autonomic:** excessive sweating. Infrequent: dry mouth, constipation, urinary retention, vision disturbance, diplopia, mydriasis, hot flushes. **Cardiovascular:** Infrequent: chest pain, hypertension, syncope, hypotension (including postural hypotension), angina pectoris, arrhythmia, tachycardia. Rare: bradycardia, ventricular arrhythmia, first degree AV block, bundle branch block, myocardial infarct, cerebral ischemia, cerebral vascular accident, thrombophlebitis. **Gastrointestinal:** nausea, disturbances of appetite, diarrhea. Infrequent: vomiting, stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, thirst, abnormal liver function tests. Rare: bloody diarrhea, hematemesis, g.i. hemorrhage, duodenal ulcer, stomach ulcer, mouth ulceration, hyperchlorhydria, colitis, enteritis, cholecystitis, cholelthiasis, hepatitis, hepatomegaly, liver tenderness, jaundice, increased salivation, salivary gland enlargement, tongue discolouration, fecal incontinence, pancreatitis. **Respiratory:** bronchitis, rhinitis, yawn. Infrequent: asthma, dyspnea, hyperventilation, pneumonia, hiccups, epistaxis. Rare: apnea, lung edema, hypoxia, pleural effusion, hemoptysis. **Endocrine:** weight loss. Infrequent: generalized edema, peripheral edema, face edema, tongue edema, hypoglycemia, hypothyroidism, weight gain. Rare: dehydration, gout, goitre, hyperthyroidism, hypercholesteremia, hyperglycemia, hyperlipemia, hyperprolactinemia, hypokalemia, hyponatremia, iron deficiency anemia, syndrome of inappropriate ADH secretion. **Hematologic:** Infrequent: anemia, lymphadenopathy, hemorrhage. Rare: bleeding time increased, leukocytosis, lymphocytosis, thrombocytopenia, thrombocytopenic purpura, thrombocythemia, retinal hemorrhage, petechia, purpura, sedimentation rate increased, aplastic anemia, pancytopenia, immune-related hemolytic anemia. **Dermatologic:** Infrequent: acne, alopecia, dry skin, herpes simplex. Rare: excema, psoriasis, seborrhea, skin hypertrophy, skin discolouration, herpes zoster, fungal dermatitis, hirsutism, ecchymoses. **Musculoskeletal:** muscle pain, back pain, joint pain. Infrequent: arthritis, bone pain, bursitis, tenosynovitis, twitching. Rare: bone necrosis, osteoporosis, pathological fracture, chrondrodystrophy, myositis, rheumatoid arthritis, muscle hemorrhage. **Urogenital:** painful menstruation, sexual dysfunction, urinary tract infection, frequent micturition. Infrequent: abnormal ejaculation, impotence, menopause, amenorrhea, menorrhagia, ovarian disorder, vaginitis, leukorrhea, fibrocystic breast, breast pain, cystitis, dysuria, urinary urgency, urinary incontinence. Rare: breast enlargement, galactorrhea, abortion, dyspareunia, uterine spasm, vaginal hemorrhage, metrorrhagia, hematuria, albuminuria, polyuria, pyuria, epididymitis, orchitis, pyelonephritis, salpingitis, urethritis, kidney calculus, urethral pain, urolithiasis. **Miscellaneous:** chills. Infrequent: amblyopia, conjunctivitis, cyst, ear pain, eye pain, jaw pain, neck pain, pelvic pain, hangover effect, malaise. Rare: abdomen enlarged, blepharitis, cataract, corneal lesion, glaucoma, iritis, ptosis, strabismus, deafness, taste loss, moniliasis, hydrocephalus, LE syndrome.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE** — There were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline. One other patient who reportedly took up to 3000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific treatment. Since vomiting occurred, the amount of drug absorbed may have been less than that ingested. Since introduction, reports of death attributed to overdosage of fluoxetine alone have been rare. **Symptoms:** Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation, including seizures.

**DOSAGE AND ADMINISTRATION** — Since it may take up to four or five weeks to reach steady-state plasma levels of PROZAC (fluoxetine), sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions. **Initial Adult Dosage:** The recommended initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited. During maintenance therapy, the dosage should be kept at the lowest effective level. A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications. **Use in the Elderly:** A lower or less frequent dosage is also recommended in the elderly. **Use in Pediatrics:** The safety and effectiveness of PROZAC in the pediatric age group has not been established.

**AVAILABILITY** — PROZAC (fluoxetine hydrochloride) 10 mg capsules are green and grey, printed with Lilly 3104 and Prozac 10 mg, packaged in amber HDPE bottles of 100. DIN 02018985

PROZAC (fluoxetine hydrochloride) 20 mg capsules are green and white, printed with Lilly 3105 and Prozac 20 mg, packaged in amber HDPE bottles of 100. DIN 00636622

PROZAC (fluoxetine hydrochloride) liquid is a clear colourless syrup solution 20 mg/5 mL, an odour of mint, packaged in amber glass bottles of 120 mL (M-5120). DIN 01917021

PROZAC is a Schedule F drug and cannot be obtained without a written order from a licensed practitioner.

**PRODUCT MONOGRAPH AVAILABLE ON REQUEST. JANUARY 22,1993**

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Scarborough, Ontario

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PAAB CCPP

Bringing Research to Life

**Intermediate Prescribing Information**

# TRANSDERM-NITRO®

(nitroglycerin)

Transdermal Therapeutic System

TRANSDERM-NITRO 0.2
Rated release *in vivo* 0.2 mg/hour, 10 cm²

TRANSDERM-NITRO 0.4
Rated release *in vivo* 0.4 mg/hour, 20 cm²

TRANSDERM-NITRO 0.6
Rated release *in vivo* 0.6 mg/hour, 30 cm²

*TRANSDERM-NITRO 0.8 (to be available in near future)
Rated release *in vivo* 0.8 mg/hour, 40 cm²

THERAPEUTIC CLASSIFICATION

Antianginal Agent

**INDICATIONS AND CLINICAL USE**

TRANSDERM-NITRO (nitroglycerin) used intermittently is indicated for the prevention of anginal attacks in patients with stable angina pectoris associated with coronary artery disease. It can be used in conjunction with other antianginal agents such as ß-blockers and/or calcium channel blockers.

TRANSDERM-NITRO is not intended for the immediate relief of acute attacks of angina pectoris. Sublingual nitroglycerin preparations should be used for this purpose.

**CONTRAINDICATIONS**

- Known hypersensitivity to nitroglycerin and related organic nitrate compounds.
- Known or suspected hypersensitivity to components of the patch.
- Acute circulatory failure associated with marked hypotension (shock and states of collapse).
- Postural hypotension.
- Myocardial insufficiency due to obstruction (e.g. in the presence of aortic or mitral stenosis or of constrictive pericarditis).
- Increased intracranial pressure.
- Increased intraocular pressure.
- Severe anemia.

**WARNINGS**

Remove TRANSDERM-NITRO before attempting cardioversion, DC defibrillation, or applying diathermy treatment, since it may be associated with damage to the paddles and burns to the patient.

Benefits and safety in angina patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use TRANSDERM-NITRO in these conditions, careful clinical or hemodynamic monitoring must be used to avoid hypotension and tachycardia.

**PRECAUTIONS**

Headaches or symptoms of hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. A reduction in dose or discontinuation of treatment may be necessary.

Exercise caution when using nitroglycerin in patients prone to, or who might be affected by hypotension (eg. volume depleted from diuretic therapy, or who have low systolic blood pressure e.g. below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of nitroglycerin, tolerance clearly occurs. There is moreover, physical dependence since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from these workers. In clinical trials of angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal.

The importance of these observations to the routine clinical use of nitroglycerin has not been fully elucidated, but patients should be monitored closely for increased anginal symptoms during drug-free periods.

Caution should be exercised in patients with arterial hypoxemia due to anemia (see CONTRAINDICATIONS), because in such patients the biotransformation of nitroglycerin is reduced. Use cautiously in patients with hypoxemia and a ventilation/perfusion imbalance due to lung disease or ischemic heart failure.

Patients with angina pectoris, myocardial infarction, or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, nitroglycerin could reverse this protective vasoconstriction and result in increased perfusion to poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen.

Tolerance to nitroglycerin with cross tolerance to other nitrates or nitrites may occur. Co-administration of other long-acting nitrates could jeopardize the integrity of the nitrate-free interval and therefore must be avoided. As tolerance to nitroglycerin patches develops, the effect of sublingual nitroglycerin on exercise tolerance, is somewhat blunted.

As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment.

*Pregnancy and Lactation*

It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman. Therefore use TRANSDERM-NITRO (nitroglycerin) only if the potential benefit justifies the risk to the fetus.

It is not known whether nitroglycerin is excreted into breast milk. Benefits to the mother must be weighed against the risks to the child.

*Pediatric Use*

Safety and effectiveness have not been established in children.

*Drug Interactions*

Concomitant treatment with other vasodilators, calcium channel blockers, ACE inhibitors, ß-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquilizers may potentiate the blood pressure lowering effect of TRANSDERM-NITRO. Dose adjustment may be necessary.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dosage adjustments of either class of agents may be necessary.

Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

Concurrent administration of TRANSDERM-NITRO with dihydroergotamine may increase the bioavailability of dihydroergotamine. Special attention should be paid to this point in patients with coronary artery disease, because dihydroergotamine antagonizes the effect of nitroglycerin and may lead to coronary vasoconstriction.

Acetylsalicylic acid and non-steroidal anti-inflammatory drugs may possibly diminish the therapeutic response to nitrates and nitroglycerin.

**ADVERSE REACTIONS**

Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Headaches may be treated with concomitant administration of mild analgesics.If such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or the product discontinued. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy.

Reddening of the skin, with or without a mild local itching or burning sensation, as well as allergic contact dermatitis may occasionally occur. Upon removal of the patch, any slight reddening of the skin will usually disappear within a few hours. The application site should be changed regularly to prevent local irritation.

Less frequently reported adverse reactions include dizziness, faintness, facial flushing, postural hypotension which may be associated with reflex tachycardia. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon. Rarely nausea, and vomiting.

**DOSAGE AND ADMINISTRATION**

*Daily Dosage Schedule:*

The daily dosage schedule is based on intermittent therapy to prevent the development of tolerance to nitroglycerin. The optimal dose should be selected based upon the clinical response, side effects and the effects of therapy on blood pressure. Starting dose is one TRANSDERM-NITRO 0.2 patch (10cm²), usually applied in the morning. If 0.2 mg/hour (l0 cm²) is well tolerated, the dose can be increased to 0.4 mg/hour (20 cm²) if required. A maximum of 0.8 mg/hour (40 cm²) may be used.

*Prevention of Tolerance:*

Although some controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e. complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustments even to levels much higher than generally used did not prevent the development of tolerance. Tolerance can be prevented or attenuated by use of an intermittent dosage schedule. Although the minimum nitrate-free interval has not been defined, clinical trials have demonstrated that a daily patch-on period of 12 - 14 hours and a daily patch-off period of 10 - 12 hours is appropriate. The patch-free time should coincide with the period in which angina pectoris is least likely to occur (usually at night). Patients should be watched carefully for an increase of angina pectoris during the patch-free period. Adjustment of background medication may be required. The dose of TRANSDERM-NITRO should be periodically reviewed in relation to continuing antianginal control.

*Site of Patch Application*

TRANSDERM-NITRO can be applied to any area of skin except the distal extremities. Many patients prefer the chest. Each successive application should be to a different site to minimize local irritation.

The area should be clean, dry, and preferably hairless. If hair is likely to interfere with patch adhesion or removal, clipping may be necessary prior to application. Take care to avoid areas with cuts or irritations.

*Composition/Description*

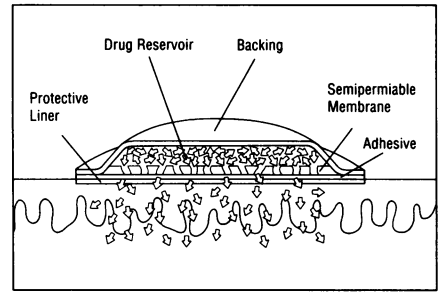
TRANSDERM-NITRO (nitroglycerin) transdermal therapeutic system, is a flat multilayer unit designed to release nitroglycerin continuously through a semipermeable membrane following its application to intact skin. In cases where permeability of the skin is excessive, drug release is limited by this release membrane.

The rate of nitroglycerin release is linearly dependent upon the drug releasing area of the applied patch (see AVAILABILITY). The nominal rate of nitroglycerin release in vivo is approximately 0.02 mg/cm²/hour. Nitroglycerin remaining in the patch serves as a thermodynamic energy source to keep the pattern of drug delivery constant.

*The patch comprises five layers:*

(1) a tan-coloured backing layer (aluminized plastic) impermeable to nitroglycerin;
(2) a drug reservoir containing nitroglycerin adsorbed on lactose, colloidal silicon dioxide and silicone medical fluid;
(3) an ethylene/vinyl acetate copolymer membrane that is permeable to nitroglycerin;
(4) a layer of hypoallergenic silicone adhesive.
(5) a protective liner (peel strip) which is removed prior to use to expose the adhesive surface.

**Cross section of the patch:**




**AVAILABILITY OF DOSAGE FORM**

| | TRANSDERM-NITRO 0.2 | TRANSDERM-NITRO 0.4 | TRANSDERM-NITRO 0.6 | TRANSDERM-NITRO 0.8 * |
|---|---|---|---|---|
| Rated Release of Nitroglycerin *in vivo* | 0.2 mg/hour | 0.4 mg/hour | 0.6 mg/hour | 0.8 mg/hour |
| Nitroglycerin Content | 25 mg | 50 mg | 75 mg | 100 mg |
| Drug Releasing Area | 10 cm² | 20 cm² | 30 cm² | 40 cm² |
| Printed Code | TRANSDERM-NITRO 0.2 MG/HR CG DOD | TRANSDERM-NITRO 0.4 MG/HR CG DPD | TRANSDERM-NITRO 0.6 MG/HR CG EJE | TRANSDERM-NITRO 0.8 MG/HR |
| Colour of Protective Liner (peel off and discard) | off-white | off-white | off-white | clear |

Store patches below 25°C. Do not freeze.

Each patch is individually sealed in a separate pouch. Do not store out of the pouch.

Keep TRANSDERM-NITRO out of reach of children and pets both before use and when disposing of used patches.

Patient Information Leaflet enclosed with each package.

Product Monograph available upon request

**Ciba, Pharmaceuticals**
Ciba-Geigy Canada Ltd./Ltée
Mississauga, Ontario L5N 2W5
or Dorval, Quebec H9S 1B1

February 1994



PAAB CCPP

# Pr Disalcid b.i.d.

(salsalate)

**NAME OF DRUG:**
Pr**DISALCID™** (salsalate)
500 mg capsules 500 and 750 mg tablets
**THERAPEUTIC CLASSIFICATION**
Anti-inflammatory analgesic agent
**ACTION AND CLINICAL PHARMACOLOGY**
Animal pharmacological studies have shown that salsalate possesses anti-inflammatory, analgesic, and antipyretic properties. Although the mechanism of the anti-inflammatory action is not clear, it seems likely that the mechanism(s) would be the same as for sodium salicylate. The anti-inflammatory effect of salicylic acid, the active *in vivo* product of Disalcid, in the treatment of arthritic disorders has been demonstrated.Therapeutic effectiveness of Disalcid in man has been demonstrated by accepted procedures, including measurements of the reduction in joint swelling, pain, and duration of morning stiffness. *In vivo*, one molecule of salsalate generates two molecules of salicylate. The hydrolysis of salsalate is accomplished by esterases present in the gastrointestinal tract, liver, plasma blood and other tissues. Following oral dosing salsalate is almost completely absorbed by the small intestine. During the process of absorption and the first pass through the liver most of the salsalate is hydrolyzed to salicylate. Unhydrolyzed salsalate appears in the urine at about 1% of the dose and about 7 to 13% as salsalate glucuronide. Clinical trials in rheumatoid arthritis and pharmacokinetic studies have shown that the anti-arthritic activity of Disalcid at 3.0 g/day is similar to that of acetylsalicylic acid (ASA) at 3.6 g/day. Disalcid 3.0 g daily induced less gastrointestinal bleeding than ASA 3.9 g daily. Disalcid is insoluble in acidic gastric fluids (<0.1 mg/mL at pH 1.0), but readily soluble in the fluids of the small intestine. Approximately 30% of the parent compound is absorbed unchanged. The remainder undergoes esterase hydrolysis in the gastrointestinal tract, liver and is absorbed as salicyclic acid. The half-life of salsalate is approximately 1 hour. About 13% is excreted through the kidneys as a glucuronide conjugate of the parent compound, another 1% as unchanged drug, and the remainder as salicylic acid and its metabolites. Only about 1% is excreted in the faeces. Salicylic acid (the primary metabolite of Disalcid) biotransformation is saturated at anti-inflammatory doses of salicylates, which results in an increase in the half-life of salicylic acid from 3.5 to 16 or more hours. Thus, dosing with Disalcid twice a day in patients will satisfactorily maintain salicylic acid blood levels within the desired therapeutic range (10 to 30 mg/100 mL) throughout the 12-hour intervals. Therapeutic blood levels continue for up to 16 hours after the last dose. The parent compound does not show capacity-limited biotransformation, nor does it accumulate in the plasma on multiple dosing.The amount of salicylic acid available from Disalcid is about 20% less than from ASA, when the two drugs are administered on a salicylic acid molar equivalent basis (3.6 g salsalate/5 g ASA). Food does not significantly affect the absorption of salsalate. Salicylic acid is a weak inhibitor of prostaglandin synthesis *in vitro*. Unlike ASA, Disalcid does not significantly affect haemostasis or cyclooxygenase activity in platelets or gastric mucosa *in vivo*.
**INDICATIONS AND CLINICAL USE**
Disalcid is indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.
**CONTRAINDICATIONS**
1.Peptic ulcer or active inflammatory disease of the gastrointestinal system. 2.Known or suspected hypersensitivity to the drug. **(See Precautions, Hypersensitivity Reactions)**
**WARNINGS**
Reye's Syndrome may develop in individuals who have chicken pox, influenza, or flu symptoms. Some studies suggest a possible association between the development of Reye's Syndrome and the use of medicines containing salicylate or ASA. Drugs containing salicylates are therefore not recommended for use in patients with chicken pox, influenza, or flu symptoms. Peptic ulceration, perforation, and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with NSAIDs including Disalcid. NSAIDs, including salicylates, should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis, or other inflammatory disease of the gastrointestinal tract. In these cases, the physician must weigh the benefits of treatment against the possible hazards. Patients taking any NSAID, including Disalcid, should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment. Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision.
**Use in Pregnancy**: Salsalate and salicylic acid have been shown to be teratogenic and embryocidal in rats when given in doses 4 to 5 times the usual human dose. These effects were not observed at doses twice as great as the usual human dose. There are no adequate and well-controlled studies in pregnant women. Disalcid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
**Labour and Delivery**: There exist no adequate and well-controlled studies in pregnant women. Although adverse effects on mother or infant have not been reported with Disalcid use during labour, caution is advised when anti-inflammatory dosage is involved. However, other salicylates have been associated with prolonged gestation and labour, maternal and neonatal bleeding sequelae, and delivery problems and stillbirth.
**Nursing Mothers:** It is not known whether salsalate per se is excreted in human milk; salicylic acid, the primary metabolite of Disalcid, has been shown to appear in human milk in concentrations approximating the maternal blood level. Thus, the infant of a mother on Disalcid therapy might ingest in mother's milk 30% to 80% as much salicylate per kg body weight as the mother is taking. Accordingly, caution should be exercised when Disalcid is administered to a nursing woman.
**PRECAUTIONS**
**Gastrointestinal System**: If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs, Disalcid should be discontinued, an appropriate treatment instituted and the patient closely monitored. There is no definitive evidence that the concomitant administration of histamine $H_2$- receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of Disalcid therapy when and if these adverse reactions appear.
**Renal Function**: Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome with NSAIDs. A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state. Over 95% of Disalcid is eliminated by the kidneys, primarily as salicylic acid and its metabolites. Therefore, the drug should be used with great caution in patients with impaired renal function. In these cases, lower doses of Disalcid should be anticipated and patients carefully monitored.During long-term therapy, patients with renal compromise should be monitored periodically.
**Hepatic Function:** As with other NSAIDs, borderline elevations of one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occurs (eg, eosinophilia, rash), this drug should be discontinued. If Disalcid is to be used in the presence of impaired liver function, it must be done under strict observation.
**Fluid and Electrolyte Balance**: Fluid retention and edema have been observed in patients treated with Disalcid. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac functions should be born in mind. Although sodium retention has not been reported in metabolic studies, Disalcid should be used with caution in patients with heart failure, hypertension, or other conditions predisposing to fluid retention. With NSAID treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; and patients receiving concomitant therapy with beta adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. In those patients who are at risk, serum electrolytes should be monitored periodically.
**Haematology**: Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when Disalcid is administered. Blood dyscrasias associated with the use of NSAIDs are rare, but could have severe consequences.
**Infection**: In common with other anti-inflammatory drugs, Disalcid may mask the usual signs of infection.
**Ophthalmology:** Blurred and/or diminished vision has been reported with the use of Disalcid and other NSAIDs. If such symptoms develop, this drug should be discontinued and an ophthalmologic examination performed.
**Central Nervous System**: The most common adverse effects associated with the central nervous system are dizziness and vertigo.
**Auditory System**: The most common side effects experienced with Disalcid are auditory. Tinnitus and temporary hearing loss have been reported with its use.
**Hypersensitivity Reactions:** Cross-reactivity, including bronchospasm, has been reported occasionally with nonacetylated salicylates, including salsalate, in ASA-sensitive patients.
**Cardiovascular Function**: Infrequent incidences of syncope and vertigo have been reported in individuals using Disalcid. In addition, hypertension and hypotension, palpitations and tachycardia have occurred.
**Other Organ Systems**: Various gastrointestinal adverse experiences are associated with Disalcid use, including nausea, abdominal pain, dyspepsia and diarrhea.
**Use in Children**: Safety and effectiveness of Disalcid use in children has not been established. **(see Warnings section)**
**Drug Interactions**: Salicylates antagonize the uricosuric action of drugs used to treat gout. ASA and other salicylate drugs will be additive to Disalcid and may increase plasma concentrations of salicylic acid to toxic levels. Drugs and foods that raise urine pH will increase renal clearance and urinary excretion of salicylic acid, thus lowering plasma levels; acidifying drugs or foods will decrease urinary excretion and increase plasma levels. The salicylate anion may displace from their binding sites other drugs which are also albumin-bound and may lead to drug interactions. For example, in patients receiving bishydroxycoumarin or warfarin, the addition of Disalcid could prolong the prothrombin time. These patients should therefore be under careful observation. Similarly, patients receiving Disalcid and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs. In addition, salicylate anion competes with a number of drugs for protein binding sites, notably penicillin, thiopental, thyroxine, triiodothyronine, sulfinpyrazone, naproxen, and possibly corticosteroids. The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations have also been reported. Salsalate and other NSAIDs may reduce the antihypertensive effect of propranolol and other beta blockers as well as other antihypertensive agents. The kinetics of salsalate are altered by concomitant administration of some antacids to the extent that urinary pH changes will affect elimination of salicylic acid and salsalate. The rate of absorption of salsalate is not adversely influenced by the presence of food. Probenecid given concurrently increases salicylic acid plasma levels and extends its plasma half-life. Caution is advised in the concomitant administration of salsalate and methotrexate since some NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, thereby possibly enhancing its toxicity.
**Clinical Laboratory Tests**: Plasma salicylic acid concentrations should be periodically monitored during long-term treatment with Disalcid to aid maintenance of therapeutically effective blood levels:
10 to 30 mg/100 mL. Toxic manifestations are not usually seen until plasma concentrations exceed 30 mg/100 mL **(see Overdosage)**.
**Drug Laboratory Test Interactions**: Salicylate competes with thyroid hormone for binding to plasma proteins, which may be reflected in a depressed plasma $T_4$ value in some patients: thyroid function and basal metabolism are unaffected.
**ADVERSE REACTIONS**
Five hundred seventy-three rheumatoid arthritis patients received salsalate in sponsored studies with a duration of 2 weeks to 1 year. Hearing and vestibular (39%), gastrointestinal (39%), body as a whole (18%), skin and appendages (13%), central and peripheral nervous system (11%), and psychiatric (6%) were the body systems (WHO nomenclature) most commonly affected (as reported by at least 5% of the study population). By WHO preferred term, the most common adverse experiences were tinnitus (31%), nausea (15%), abdominal pain (14%), dyspepsia (12%), headache (11%), rash (9%), hearing loss (9%), dizziness (8%), diarrhea (7%), deafness (5%), and constipation (5%). Adverse experiences were followed to resolution, and no residual effects were known to have occurred. Spontaneous reports reflecting US marketing experience over 14 years are available. The precise number of patients treated is unknown; it is not possible to determine an overall incidence of any particular adverse event. These data show a modest number of reports dealing with adverse events that may be medically serious, eg, renal and hepatic dysfunction including hepatitis; gastrointestinal haemorrhage; bronchospasm; anaphylactic shock; and death. Causality with salsalate treatment is often difficult to ascertain. Of the seven deaths reported, only three could probably be ascribed to salsalate. Two of these deaths were due to bronchospasm (one likely was laryngospasm). Another death was caused by salicylate intoxication due to iatrogenic overdose. The US system of reporting adverse events to the manufacturer generally selects for the most serious events; however, the frequency of all reports with the use of Disalcid averaged less than one report per million patient days (based on an average daily dose of 3 g). Tinnitus has been reported most frequently, as noted in sponsored multicenter efficacy/safety studies. This adverse experience is typical of salicylates. The detailed breakdown of side effects with corresponding frequencies (no frequency indicated if <1%) from the above sponsored studies follows. (The frequencies observed in the placebo group [N=73] in one study are also indicated by system except if 0%.)
**Hearing and Vestibular (39% vs 4% for Placebo)**: Tinnitus (31%), hearing loss (9%), deafness (5%), earache (1%), dysacusis (1%).

**Gastrointestinal (39% vs 16% for Placebo)**: Nausea (15%), abdominal pain (14%), dyspepsia (12%), diarrhea (7%), constipation (5%), flatulence (3%), vomiting (2%), stomatitis (2%), haemorrhage rectum (1%), melena (1%), dysphagia (1%), anorexia, gastroenteritis, GI disorders (unspecified), colitis, eructation, gastric ulcer, haemorrhoids, hiatus hernia, hiccup, stomatitis ulcerative.
**Body as a Whole (18% vs 11% for Placebo)**: Headache (11%), edema (4%), fatigue (2%), chest pain (2%), pain (1%), fever (1%), therapeutic response increased, rigors, asthenia, abdomen enlarged, malaise.
**Skin and Appendages (13% vs 3% for Placebo)**: Rash (9%), pruritus (3%), dermatitis (1%), skin disorder (1%), acne, alopecia, angioedema, eczema, erythema, hair texture abnormal, rash maculopapular, skin hypertrophy, urticaria.
**Central and Peripheral Nervous System (11% vs 4% for Placebo)**: Dizziness (8%), vertigo (3%), ataxia (1%), leg cramps, paraesthesia, migraine, hyperaesthesia, hypertonia, tremor, twitching.
**Psychiatric (6% vs 4% for Placebo)**: Somnolence (2%), insomnia (1%), depression (1%), confusion (1%), anxiety (1%), amnesia, euphoria, nervousness.
**Liver and Biliary (4%)** : Hepatic function abnormal (4%), transaminase increased.
**Respiratory (4%)**: Dyspnea (1%), rhinitis (1%), coughing (1%), sinusitis (1%), upper respiratory tract infection (1%), bronchitis, bronchospasm, hyperventilation, pharyngitis, respiratory disorder.
**Autonomic Nervous System (3%)**: Flushing (1%), sweating increased (1%), mouth dry (1%), skin cold clammy.
**Vision (2% vs 1% for Placebo)**: Eye abnormality (1%), diplopia, conjunctivitis, eye pain, iritis, vision abnormal.
**Cardiovascular, General (1%)**: Syncope, hypertension, hypotension.
**Heart Rate and Rhythm (1%)**: Palpitations (1%), tachycardia.
**Metabolic and Nutritional (1% vs 1% for Placebo)**: Weight increase (1%), thirst, enzyme abnormality, thyroid function tests abnormal, weight decrease.
**Platelet, Bleeding and Clotting (1%)**: Epistaxis, prothrombin decreased, thrombocytopenia.
**Resistance Mechanism (1%)**: Herpes simplex, infection, otitis media.
**Special Senses Other (1%)**: Taste perversion (1%), taste loss.
**Urinary (1%)**: Urinary tract infection (1%), haematuria, pyuria, urinary incontinence, dysuria, polyuria.
**Vascular (Extracardiac)(1%)**: Purpura.
**White Cell and Resistance (1%)**: Leucopenia (1%), lymphadenopathy.
**Red Blood Cell**: Anaemia.
**Reproductive, Female**: Menorrhagia.
**Musculoskeletal**: Arthralgia

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Death has followed ingestion of 10 to 30 g of salicylates in adults, but much larger amounts have been ingested without fatal outcome.
**Symptoms**: The usual symptoms of salicylism (tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting and diarrhea) will occur. More severe intoxication will lead to disruption of electrolyte balance and blood pH, hyperthermia and dehydration.
**Treatment**: Further absorption of Disalcid from the gastroinestinal tract should be prevented by emesis (syrup of ipecac), and, if necessary, by gastric lavage. Fluid and electrolyte imbalance should be corrected by the administration of appropriate IV therapy. Adequate renal function should be maintained. Haemodialysis or peritoneal dialysis may be required in extreme cases.

**DOSAGE AND ADMINISTRATION**

**Adults**: The usual dosage is 3000 mg daily, given in divided doses as follows; 1) two doses of two 750 mg tablets; 2) two doses of three 500 mg tablets; or 3) three doses of two 500 mg tablets. Some patients, eg. the elderly, may require a lower dosage to achieve therapeutic blood concentrations and to avoid the more common side effects such as tinnitus. Alleviation of symptoms is gradual and full benefit may not be evident before two weeks. There is no evidence for development of tissue tolerance (tachyphylaxis), but salicylate therapy may induce increased activity of metabolizing liver enzymes, causing a greater rate of salicyluric acid production and excretion with a resultant increase in dosage requirement for maintenance of therapeutic serum salicylate levels.
**Children:** Dosage recommendations and indications for Disalcid use in children have not been established.

**AVAILABILITY**

Disalcid is available as: **Tablets:** 500 mg, round, aqua, scored, film-coated tablet imprinted with "3M" on one side and "Disalcid" on the other. Bottles of 100. 750 mg, capsule-shaped, aqua, scored, film-coated tablet imprinted with "3M" on one side and "Disalcid 750" on the other. Bottles of 100.

**REFERENCES**:


1.Roth S, Bennett R, Caldron P, Hartman R, Mitchell C, Doucette M, et al. Reduced risk of NSAID gastropathy (GI mucosal toxicity) with nonacetylated salicylate (salsalate): an endoscopic study. Seminars in arthritis and rheumatism 1990;19(4 Suppl 2):11-9.
2.Cryer B, Goldschmiedt M, Redfern JS, Feldman M. Comparison of salsalate and aspirin on mucosal injury and gastroduodenal mucosal prostaglandins. Gastroenterology 1990;99:1616-21.
3.Flower RJ, Moncada S, Vane JR. Analgesic-antipyretics and anti-inflammatory agents; Drugs employed in the treatment of gout. In: Goodman Gilman A, Goodman LS, Rall TW, Murad F, editors. The Pharmacological Basis of Therapeutics. Seventh Edition. New York: Macmillan Publishing Company, 1985:674-715.
4.Morris HG, Sherman NA, McQuain C, Goldlust MB, Chang SF, Harrison LI. Effects of salsalate (nonacetylated salicylate) and aspirin on serum prostaglandins in humans. Ther Drug Monitor 1985;7:435-8.
5.Roth SH, Bennett RE. Nonsteroidal anti-inflammatory drug gastropathy - recognition and response. Arch Intern Med 1987;147:2093-100.
6.April PA, Abeles M, Baraf HSB, Cohen SA, Curran NJ, Doucette BS, et al. Does the acetyl group of aspirin contribute to the antiinflammatory efficacy of salicylic acid in the treatment of rheumatoid arthritis? J Rheumatol 1989;16:321-7.
7.Product Monograph: Disalcid (salsalate). 3M Pharmaceuticals. 3M Canada Inc.


Product monograph available upon request

"Disalcid™ b.i.d.
(salsalate)

Innovation working for you™


**3M Pharmaceuticals**
**3M Canada Inc.**
Post Office Box 5757
London, Ontario N6A 4T1


3M

"proctosedyl® HC
(Hydrocortisone BP - Framycetin sulphate BP - Cinchocaine hydrochloride BP - Aesculin)

**To the rescue when every second counts.**

**Prescribing Information**

**Indications:** The reduction of swelling, pain and inflammation of hemorrhoids and other rectal lesions. The management of acute and chronic nonspecific proctitis, acute internal hemorrhoids, cryptitis, fissures and incomplete fistulas, internal and external pruritus ani. May be used in pre- and post-operative hemorrhoidectomy and repair of fissures.

**Contraindications:** Hydrocortisone must not be used in the presence of tuberculosis, fungal and viral infections. Sensitivity to any of the components.

**Precautions:** Discontinue use if sensitization occurs. Hydrocortisone should not be used until an adequate proctologic examination is completed and a diagnosis made. Other specific measures against infections, allergy, and other causal factors must not be neglected. The possibility, however rare, that prolonged use of this preparation might produce systemic corticosteroid effects, should be borne in mind. Patients should be advised to inform subsequent physicians of the previous use of hydrocortisone. The safe use of topical corticosteroids during pregnancy has not been fully established. Therefore, during pregnancy they should not be used unnecessarily on extended areas, in large amounts or for prolonged periods of time.

**Adverse effects:** Certain patients may experience burning upon application, especially if the mucous membrane is not intact.

**Dosage:** *Ointment:* For external treatment: Apply a small quantity morning and evening and after each bowel movement, to the affected area. For internal application: attach rectal cannula to tube, insert to full extent and squeeze tube gently from lower end whilst withdrawing. *Suppositories:* 1 suppository morning and evening and after each bowel movement.

**Supplied:** Each rectal suppository or g of ointment contains: hydrocortisone BP 5 mg (0.5%), framycetin sulphate BP 10 mg (equivalent to 7 mg of framycetin base – 1%), cinchocaine HCl BP 5 mg (0.5%), aesculin 10 mg (1%). The ointment contains 10% w/w anhydrous lanolin. Ointment, tubes of 15 and 30 g with rectal cannula; suppositories, boxes of 12 and 24. Store at cool temperature.

**References:**


1. Adriani J et al. Clin Pharmacol Thera. 1964, 5:49.


ROUSSEL
ROUSSEL CANADA INC.
MONTREAL, QUEBEC

# Pr VASOTEC®

**(enalapril maleate, Frosst Std.)**

**Tablets 2.5, 5, 10, 20 mg**

**Angiotensin Converting Enzyme Inhibitor**

## INDICATIONS AND CLINICAL USE

The treatment of essential or renovascular hypertension; usually administered in association with other drugs, particularly thiazide diuretics. Consider the risk of angioedema (see WARNINGS). Normally used when a diuretic or beta-blocker was ineffective or associated with unacceptable adverse effects. Can also be tried as initial agent where a diuretic and/or beta-blocker is contraindicated or could cause serious adverse effects.

Also indicated in the treatment of congestive heart failure, as adjunctive therapy in patients not responding adequately to digitalis and diuretics.

**Use of ACE inhibitors during the second and third trimesters of pregnancy can cause injury or death of a developing fetus. When pregnancy is detected, discontinue VASOTEC® as soon as possible (see WARNINGS; Use in Pregnancy).**

## CONTRAINDICATIONS

Hypersensitivity to any component; history of angioneurotic edema related to ACE inhibitor therapy.

## WARNINGS

**Angioedema,** with laryngeal edema and/or shock, have been reported and may be fatal. In such cases, discontinue drug promptly and observe patient until swelling subsides. Swelling confined to the face, lips, and mouth usually resolves without treatment, although antihistamines may be useful in relieving symptoms. However, where there is involvement of the tongue, glottis and larynx, likely to cause airway obstruction, prompt administration of subcutaneous adrenaline (0.5mL 1:1000) may be indicated. Patients with a history of angioedema, unrelated to ACE inhibitor use, may be at increased risk (see CONTRAINDICATIONS).

**Symptomatic hypotension** has occurred, usually during initial therapy or when the dose was increased, and is more likely in patients who are volume-depleted. In patients with severe congestive heart failure, excessive hypotension may be associated with oliguria and/or progressive azotemia. For patients in whom the excessive hypotension could result in severe or fatal complications, i.e. those with severe congestive heart failure, ischemic heart or cerebrovascular disease – start therapy under close medical supervision, usually in a hospital. Such patients should be followed closely for the potential fall in blood pressure during first two weeks of therapy or when enalapril or a diuretic is increased. If hypotension occurs, place patient in supine position and if needed, administer IV infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of enalapril.

**Neutropenia/agranulocytosis** and bone marrow depression have been caused by ACE inhibitors. Current experience with enalapril shows incidence to be rare. Consider periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease.

**Use of ACE inhibitors in pregnancy** can cause fetal and neonatal morbidity and mortality. When pregnancy is detected, discontinue VASOTEC® as soon as possible. Rarely, no alternatives to an ACE inhibitor will be found and mothers should be apprised to the potential hazards to the fetus. Ultrasound should be performed to assess fetal development, well-being and volume of amniotic fluid. If oligohydramnios is observed, discontinue VASOTEC® unless lifesaving for the mother. A non-stress test and/or a biophysical profiling may be appropriate; however, if concerns persist, a contraction stress testing should be considered. Oligohydramnios may only appear after fetus has sustained irreversible injury.

Closely observe infants exposed *in utero* to ACE inhibitors for hypotension, oliguria and hyperkalemia, and initiate appropriate corrective medical procedures.

**Human Data:** Exposure to ACE inhibitors during second and third trimesters has been associated with hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death of the fetus. Oligohydramnios, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development also has been reported. Prematurity and patent ductus arteriosus also reported but unknown if due to ACE inhibitor use. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

## PRECAUTIONS

**Impaired renal function:** Renal function should be assessed before initiating therapy with enalapril. Patients with renal insufficiency may require reduced or less frequent doses, and their renal function must be monitored appropriately (see DOSAGE). Renal failure, which has been reported mainly in patients with severe heart failure or underlying renal disease including renal artery stenosis, is usually reversible when treated promptly.

Some hypertensive patients with no apparent renal disease have developed increases in BUN and creatinine while on concurrent diuretic/enalapril therapy. Dosage reduction or discontinuation of one or both drugs may be required.

**Hyperkalemia:** In clinical trials, hyperkalemia (>5.7 mmol/L) was observed in approximately 1% of hypertensive patients, and caused discontinuation of therapy in 0.28% of such patients. Risk factors for hyperkalemia development may include renal insufficiency, diabetes mellitus, and concomitant use of agents to treat hypokalemia (see ADVERSE REACTIONS).

**Valvular Stenosis:** Theoretically, patients with aortic stenosis, who do not develop as much afterload reduction, might be at risk of decreased coronary perfusion when treated with vasodilators.

**Surgery/Anaesthesia:** During major surgery or anaesthesia with hypotensive agents, enalapril blocks angiotensin II formation secondary to compensatory renin release. Hypotension that develops due to this mechanism can be corrected by volume expansion.



**Impaired liver function:** Hepatitis, jaundice (hepatocellular and/or cholestatic), elevation of liver enzymes and/or serum bilirubin, which have occurred in patients with or without pre-existing liver abnormalities, were usually reversed on discontinuation of enalapril. For any unexplained symptoms, particularly within the first months of treatment, a full set of liver function tests and other necessary investigations are recommended. Consider discontinuation of enalapril when appropriate. Use enalapril with particular caution in patients with pre-existing liver abnormalities. Obtain baseline liver function tests before initiating therapy and monitor response and metabolic effects closely.

**Cough:** A dry, persistent cough has been reported, which usually disappears after withdrawal or lowering the dose of enalapril.

**Nursing mothers:** Enalapril is secreted in human milk in trace amounts therefore, nursing should be interrupted.

**Pediatric use:** This use is not recommended because enalapril has not been studied in children.

**Anaphylactoid Reactions during Membrane Exposure:** Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (eg. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. If symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur, stop dialysis immediately. The symptoms are not relieved by antihistamines and the use of a different type of dialysis membrane or class of antihypertensive agent should be considered.

**Anaphylactoid Reactions during Desensitization**
Isolated reports of sustained life threatening anaphylactoid reactions during desensitizing treatment with hymenoptera (bees, wasp) venom in patients receiving ACE inhibitors. These reactions have been avoided when ACE inhibitors were withheld for 24 hours but have reappeared upon inadvertent rechallenge.

**Drug Interactions**
**Hypotension - Patients on Diuretic Therapy:** Particularly when diuretics recently initiated, patients occasionally experience hypotension after initiating therapy with enalapril. To minimize the hypotensive effects, discontinue the diuretic or increase the salt intake prior to starting the drug (see WARNINGS).

**Agents Increasing Serum Potassium:** Since enalapril decreases aldosterone production, elevation of serum potassium may occur. Diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given cautiously for documented hypokalemia only and should be monitored frequently. Potassium containing salt substitutes should be used with caution.

**Agents Causing Renin Release:** Diuretics, for example, augment the antihypertensive effect of enalapril.

**Agents Affecting Sympathetic Activity:** Ganglionic blocking agents or adrenergic neuron blocking agents, for example, may be used with caution. Beta-adrenergic blockers add some further antihypertensive effect to enalapril.

**Lithium Salts:** Lithium clearance may be reduced; therefore, monitor serum lithium levels carefully if they are administered.

## ADVERSE REACTIONS

In controlled clinical trials involving 2314 hypertensive patients and 363 heart failure patients, the most severe adverse reactions were: angioedema (0.2%), hypotension (2.3%) and renal failure (5 cases). In hypertensive patients, hypotension occurred in 0.9% and syncope in 0.5%, with a discontinuation rate of 0.1%. In heart failure patients, hypotension occurred in 4.4% and syncope in 0.8%, with a discontinuation rate of 2.5%. The most frequent clinical adverse reactions in controlled clinical trials were: headache (4.8%), dizziness (4.6%) and fatigue (2.8%). Discontinuation of therapy was required in 6.0% of the 2677 patients.

| | Hypertension % (2314 Patients) | Heart Failure % (363 Patients) |
|---|---|---|
| **CARDIOVASCULAR** | | |
| Hypotension | 0.9 | 4.4 |
| Chest Pain | 0.9 | 1.7 |
| Palpitations | 0.6 | 0.3 |
| Myocardial Infarction, Acute | 0.2 | 0.6 |
| Myocardial Infarction, Recurrent | — | 0.3 |
| **GASTROINTESTINAL** | | |
| Nausea | 1.4 | 1.1 |
| Vomiting | 0.8 | 1.7 |
| Dysphagia | 0.1 | — |
| Diarrhea | 1.4 | 3.0 |
| Abdominal pain | 0.7 | 1.4 |
| **RENAL** | | |
| Renal failure | 0.1 | 0.6 |
| Oliguria | 1 case | — |
| Proteinuria† | 0.1 | — |
| **DERMATOLOGIC** | | |
| Rash | 1.4 | 1.9 |
| Pruritus | 0.4 | 1.4 |
| **NERVOUS SYSTEM** | | |
| Headache | 5.2 | 2.2 |
| Dizziness | 4.3 | 6.6 |
| Insomnia | 0.5 | 0.3 |
| Nervousness | 0.6 | — |
| Somnolence | 0.6 | — |
| Paresthesia | 0.6 | — |
| **ALLERGIC** | | |
| Cough | 1.3 | 1.4 |
| Angioedema | 0.2 | — |
| **HEMATOLOGIC** | | |
| Anemia | 0.1 | — |
| Leukopenia | 1 case | — |
| **MISCELLANEOUS** | | |
| Muscle cramps | 0.6 | 0.3 |
| Dyspnea | 0.6 | 1.1 |
| Hyperhidrosis | 0.7 | — |
| Impotence | 0.4 | 0.3 |
| Fatigue | 3.0 | 1.4 |
| Taste disturbance | 0.4 | 0.3 |

† Defined as >1 g/24h or >0.5 g/12h on two consecutive measurements, at least one month apart.

**ABNORMAL LABORATORY FINDINGS**

**Hyperkalemia:** (see PRECAUTIONS).

**Creatinine, Blood Urea Nitrogen:** Increases were reported in about 20% of patients with renovascular hypertension and about 0.2% of patients with essential hypertension on enalapril alone. Increases, which usually were reversible upon discontinuation of enalapril or concomitant therapy, were reported in 9.7% of heart failure patients who were receiving diuretics and/or digitalis.

**Hemoglobin and Hematocrit:** Decreases (mean approximately 0.34 g% and 1.0 vol%, respectively) occurred frequently, but were rarely of clinical importance. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

**Hepatic:** Elevations of liver enzymes and/or serum bilirubin have occurred (see PRECAUTIONS).

**ADVERSE REACTIONS REPORTED IN UNCONTROLLED TRIALS AND/OR MARKETING EXPERIENCE**

**With an incidence of 0.5 to 1%:** Insomnia, impotence, renal dysfunction, renal failure and oliguria.

**With an incidence < 0.5%:**
**Cardiovascular:** Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS); cardiac arrest; pulmonary embolism; rhythm disturbances; angina pectoris. **Gastrointestinal:** Anorexia; ileus; pancreatitis; dyspepsia; constipation. **Hemopoeitic:** Neutropenia; thrombocytopenia; bone marrow depression. **Hepatic:** Liver function abnormalities; hepatitis; jaundice (hepatocellular and/or cholestatic). **Nervous System/Psychiatric:** Vertigo; depression; confusion; ataxia. **Respiratory:** Bronchospasm/asthma; rhinorrhea. **Other:** Erythema multiforme; exfoliative dermatitis; Stevens-Johnson syndrome; toxic epidermal necrosis; urticaria; photosensitivity; alopecia; flushing; tinnitus; hearing impairment; glossitis; blurred vision. A symptom complex has been reported which may include fever, serositis, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

**LABORATORY TEST FINDINGS:** Hyponatremia

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited human data are available. The most likely manifestation of overdosage would be hypotension, which can be treated by I.V. infusion of normal saline solution. Enalaprilat may be removed from the general circulation by hemodialysis.

## DOSAGE AND ADMINISTRATION

Dosage must be individualized. The absorption of enalapril maleate is not affected by food.

**HYPERTENSION**

Initiation of enalapril requires consideration of extent of blood pressure elevation, salt restriction and recently used antihypertensive agents, the dosage of which may need to be adjusted.

The recommended initial dose of enalapril maleate in patients not on diuretics is 5 mg once a day. Adjust dosage according to blood pressure response; the usual range is 10 to 40 mg daily, in a single dose or divided in two doses. Some patients on once-daily dosage may have diminished antihypertensive effect toward the end of dosing interval and require an increase in dosage, or twice daily administration. If blood pressure is not controlled, a diuretic may be added. Raising the daily dose above 40 mg is not recommended because adverse reactions may be increased.

Occasionally symptomatic hypotension may occur following the initial dose, more likely in patients currently taking a diuretic. Therefore, if possible, discontinue the diuretic two to three days before initiating enalapril therapy (see WARNINGS). If the diuretic cannot be discontinued, use an initial dose of 2.5 mg.

In the absence of sufficient experience in the treatment of accelerated or malignant hypertension, enalapril is not recommended in such situations.

**Dosage in the Elderly (over 65 years):** Start at 2.5 mg daily. Some elderly patients may be more responsive than younger patients.

**Dosage Adjustment in Renal Impairment:** (see PRECAUTIONS-Anaphylactoid Reactions during Membrane Exposure)

Guidelines for reducing doses in hypertensive patients:

| Renal Status | Creatinine Clearance mL/min(mL/s) | Initial Dose mg/day |
|---|---|---|
| Normal renal function | >80 mL/min (>1.33 mL/s) | 5 mg |
| Mild impairment | ≤80>30 mL/min (≤1.33>0.50 mL/s) | 5 mg |
| Moderate to severe impairment | ≤30 mL/min (≤0.50 mL/s) | 2.5 mg |
| Dialysis patients | — | 2.5 mg on dialysis days* |

* Enalaprilat is dialysable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

**CONGESTIVE HEART FAILURE**

Use in conjunction with a diuretic and digitalis. Initiate therapy under close medical supervision, usually in a hospital. Monitor blood pressure and renal function before and during treatment with enalapril, because severe hypotension, and more rarely, consequent renal failure have been reported (see WARNINGS and PRECAUTIONS).

When initiating enalapril consider the recent diuretic therapy and possibility of severe salt/volume depletion. Before beginning enalapril reduce diuretic therapy if possible.

The recommended initial daily dose is 2.5 mg. While managing symptomatic hypotension, increase dose gradually, depending on individual response, to the usual maintenance dose of 10-20 mg daily, given in a single dose or divided in two doses. This dose titration may be performed over a two- to four-week period, or more rapidly if indicated by residual signs and symptoms of heart failure. The maximum daily dose is 40 mg.

## AVAILABILITY OF DOSAGE FORMS

Barrel-shaped, biconvex tablets, engraved with code number on one side and VASOTEC on other.

VASOTEC® 2.5 mg - yellow, scored, engraved 14.

VASOTEC® 5 mg - white, scored, engraved 712.

VASOTEC® 10 mg - rust-red, engraved 713.

VASOTEC® 20 mg - peach, engraved 714.

All strengths available in blisters of 30 and bottles of 100 tablets.

**PRODUCT MONOGRAPH AVAILABLE ON REQUEST**

(497x-a,9,93)


**References for 5527**

1. SOLVD Investigators. Effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med Aug 1, 1991;325:293-302.
2. CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med June 4, 1987; 316:1429-1435.

5527, 5959, 5973, 5974, 7457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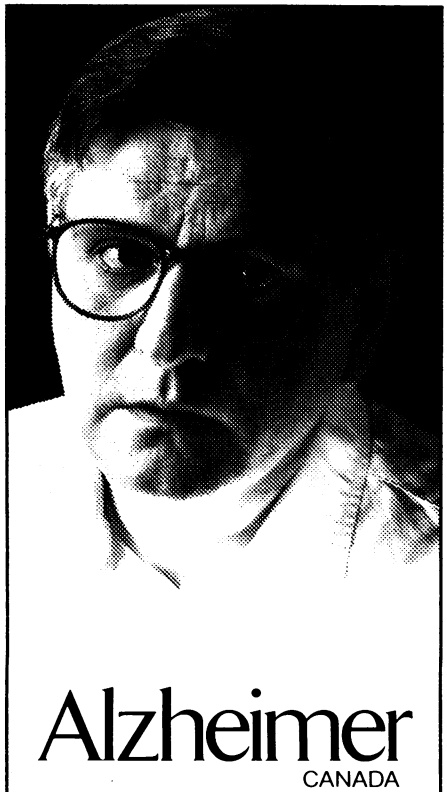



# Pr ZOCOR®

## (simvastatin tablets)

**Tablets 5 and 10 mg**

**Cholesterol-lowering agent**

## INDICATIONS AND CLINICAL USE

As an adjunct to diet for the reduction of elevated total and LDL-C levels in patients with primary hypercholesterolemia; also in combined hypercholesterolemia and hypertriglyceridemia, when hypercholesterolemia is the abnormality of most concern.

To determine which patients to treat, initially establish that the elevation in plasma lipids is not due to underlying conditions such as poorly-controlled diabetes mellitus, hypothyroidism, the nephrotic syndrome, liver disease, or dysproteinemias. Then ascertain whether elevated LDL-C level is the cause for elevated total serum cholesterol, particularly in patients with total triglycerides over 4.52 mmol/L (400 mg/dL) or with markedly elevated HDL-C values, where non-LDL lipoprotein fractions may contribute significantly to total cholesterol levels, without apparent increase in cardiovascular risk.

## CONTRAINDICATIONS

Hypersensitivity to any component. Active liver disease or unexplained persistent elevations of serum transaminases. Pregnancy and lactation (see PRECAUTIONS).

## WARNINGS

**The effects of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality have not been established.**

**1. Hepatic effects: In clinical trials, marked persistent increases in serum transaminases occurred in 1% of adult patients who received simvastatin (see ADVERSE REACTIONS).** Increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Serum transaminases fell slowly to pre-treatment levels when drug was interrupted or discontinued.

**All patients should have liver function tests at baseline and periodically thereafter.** Patients who develop elevated serum transaminase levels require special attention, prompt retesting and more frequent testing.

**Discontinue drug if transaminase levels show evidence of progression, particularly a rise to 3 times the upper limit of normal that persists.**

Use with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Discontinue drug if active liver disease or unexplained persistent transaminase elevations develop during therapy (see CONTRAINDICATIONS).

Moderate elevations of serum transaminases, reported with simvastatin, have also been observed with other, comparative lipid-lowering agents. These changes generally appeared within the first 3 months after initiation of therapy, were often transient, not accompanied by any symptom, and did not need interruption of treatment.

**2. Muscle Effects - CPK:** Transient elevation of creatine phosphokinase (CPK) levels commonly seen, usually have no clinical significance. - **Myalgia** and muscle cramps have also been observed. - **Myopathy** reported rarely (0.05%); consider possibility in any patient with diffuse myalgias, muscle tenderness and/or marked elevation of creatine phosphokinase (≥ 10 times the upper limit of normal). Ask patients to promptly report unexplained muscle pain, tenderness and weakness. With *lovastatin*, a closely related HMG-CoA reductase inhibitor, the risk of myopathy is known to be substantially increased by concomitant immunosuppressive drugs including cyclosporins, or gemfibrozil or lipid-lowering doses of niacin. Severe rhabdomyolysis that precipitated acute renal failure was reported. Also, rhabdomyolysis with or without renal impairment was reported in seriously ill patients receiving concomitant erythromycin and lovastatin.

Therefore, carefully consider benefits and risks of concomitant use of simvastatin with immunosuppressive drugs, fibrates, erythromycin or lipid-lowering doses of niacin. Consider interrupting simvastatin in any patient with an acute, serious condition, suggestive of a myopathy or a risk factor predisposing to development of renal failure or rhabdomyolysis, such as: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.

## PRECAUTIONS

**General:** Before starting therapy, attempt to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat underlying medical problems (see INDICATIONS). The patient should inform subsequent physicians of prior use of simvastatin. **Ophthalmic evaluations:** Current data do not indicate adverse effects on the human lens, but long-term effects have not been established. Periodic ophthalmological exams are recommended, keeping in mind that even without drugs, an increased prevalence in lens opacities could be expected with aging. **Use in homozygous familial hypercholesterolemia:** simvastatin is unlikely to be of clinical benefit. **Effect on Lipoprotein(a) [Lp(a)]:** In some patients, the beneficial lowering of total and LDL cholesterol may be partly blunted by increased Lp(a) levels. Pending further experience, Lp(a) plasma levels should be measured when feasible in patients given simvastatin. **Hypersensitivity:** A few instances of eosinophilia and skin eruptions appear to be associated with simvastatin. If hypersensitivity suspected, discontinue drug. **Carcinogenesis:** In animal studies, increased incidences of hepatocellular adenomas and carcinomas, pulmonary adenomas and harderian gland adenomas were noticed in mice receiving 500 times the maximum recommended human dose. Female rats receiving 31 times the maximum recommended human dose exhibited an increased incidence of thyroid follicular adenomas. (See TOXICOLOGY Section of Product Monograph.)

**Use in obstetrics: Simvastatin is contraindicated during pregnancy** and there are no data on such use. Because the HMG-CoA reductase inhibitors are able to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway that are essential components for fetal development, simvastatin may cause fetal harm. Administer to women of childbearing age only when they are highly unlikely to conceive. If a patient becomes pregnant, apprise her of potential hazard to the fetus, and discontinue drug. **Nursing mothers:** Whether simvastatin is excreted in human milk is unknown. However, because of the potential for serious adverse reactions, women taking simvastatin should not nurse (see CONTRAINDICATIONS). **Pediatric use:** Safety and effectiveness have not been established; therefore simvastatin therapy in children is not yet recommended. **Use in patients with impaired renal function:** Exercise caution if renal function impairment is significant.

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**Drug Interactions**

**Concomitant therapy with other lipid-lowering agents:** Cholesterol-lowering effects of simvastatin and cholestyramine appear additive. Exercise caution when coadministering with other lipid-lowering agents, particularly gemfibrozil and niacin (see WARNINGS). **Erythromycin:** See WARNINGS: Muscle effects. **ACE Inhibitors:** Hyperkalemia associated with myositis was reported in a single patient with insulin-dependent diabetes mellitus and mild renal insufficiency who received another HMG-CoA reductase inhibitor: lovastatin with an ACE inhibitor, lisinopril. **Coumarin anticoagulants:** Determine prothrombin time in patients on concomitant coumarin anticoagulants before starting simvastatin therapy and monitor periodically, because anticoagulant effect of warfarin appeared to be slightly enhanced by simvastatin use. **Digoxin:** Digoxin plasma concentrations were slightly elevated by coadministration of simvastatin. **Propranolol:** No clinically significant pharmacokinetic or pharmacodynamic interaction noted with concomitant simvastatin. **Antipyrine:** Simvastatin had little or no effect on the pharmacokinetics of antipyrine. **Other concomitant therapy:** Exercise caution with coadministration of immunosuppressants (see WARNINGS). In clinical studies, simvastatin was used with beta-blockers, calcium-channel blockers, diuretics and NSAIDs, without evidence of clinically significant adverse interactions.

**Drug/laboratory test interactions:** Simvastatin may elevate serum transaminase and creatine phosphokinase levels (see ADVERSE REACTIONS). In differential diagnosis of chest pain in patients on simvastatin, determine cardiac and non-cardiac fractions of these enzymes.

## ADVERSE REACTIONS

Simvastatin was found generally well tolerated, and adverse reactions usually mild and transient, based on experience in over 2300 patients, of whom over 1200 were treated for 1 year and over 230 for 2 years or more. In controlled clinical trials, 1% were withdrawn due to adverse experiences attributable to simvastatin. Adverse experiences occurring at an incidence of ≥0.5% of 2361 patients treated with simvastatin in controlled clinical studies and reported to be possibly, probably or definitely drug related are shown in the table below:

| | ZOCOR® (n = 2361) % |
|---|---|
| **Gastrointestinal** | |
| Acid Regurgitation | 0.5 |
| Constipation | 2.5 |
| Dyspepsia | 0.6 |
| Diarrhea | 0.8 |
| Flatulence | 2.0 |
| Nausea | 1.1 |
| **Nervous System** | |
| Headache | 1.0 |
| **Skin** | |
| Rash | 0.7 |
| **Miscellaneous** | |
| Abdominal Pain | 2.2 |
| Asthenia | 0.8 |

**Ophthalmological Observations:** see PRECAUTIONS.

**Laboratory tests:** Marked persistent increases of serum transaminases noted (see WARNINGS). About 5% of patients had elevations of CPK levels of at least three times normal value, attributable to the non-cardiac fraction of CPK, on one or more occasions. Myopathy reported rarely (see WARNINGS and PRECAUTIONS).

**Others:** Though not observed in clinical trials with simvastatin, the following have been reported with other HMG-CoA reductase inhibitors: hepatitis, cholestatic jaundice, vomiting, anorexia, paresthesia, psychic disturbances including anxiety, and hypospermia. Also reported rarely with lovastatin was a hypersensitivity syndrome which included one or more of the following: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever and malaise.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

No experience of deliberate or accidental overdosage. **Treatment** should be symptomatic and supportive; liver function should be monitored, and appropriate therapy instituted. Dialyzability of simvastatin not known.

## DOSAGE AND ADMINISTRATION

Before initiating simvastatin, place patient on standard cholesterol-lowering diet, and continue on this diet during treatment. If appropriate, implement a program of weight control and exercise. **Usual starting dose**: 10 mg/day, as a single dose in the **evening.** Make dosage adjustments, if necessary, at intervals of not less than 4 weeks, to **maximum** of 40 mg daily, given as a single evening dose. **Monitor cholesterol levels periodically and consider reducing dosage if cholesterol levels fall below targeted range, as recommended by the Canadian Consensus Conference on Cholesterol.**

**Concomitant therapy:** Cholesterol-lowering effects of simvastatin and cholestyramine appear additive. For use with other lipid-lowering agents, see WARNINGS and PRECAUTIONS.

## AVAILABILITY AND DOSAGE FORMS

ZOCOR® Tablets are shield-shaped, film-coated, engraved with a code on one side and Z on the other. Both strengths are available in blister packs of 30 tablets. 10 mg tablets also available in bottles of 500s.

- ZOCOR® 5 mg, buff tablet, engraved 726.
- ZOCOR® 10 mg, peach tablet, engraved 735.

## PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(498x-a,9,93)


**References**

1. Malini PL et al.: Simvastatin versus pravastatin: Efficacy and tolerability in patients with primary hypercholesterolemia. Clin Ther 1991;13(4): 500-510.
2. Data on file, Merck Frosst Canada Inc., April 1992.

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# PrINHIBACE™ (cilazapril)

### Therapeutic Classification

Angiotensin Converting Enzyme Inhibitor

### Actions and clinical pharmacology

'Inhibace' (cilazapril) is an angiotensin converting enzyme (ACE) inhibitor, which is used in the treatment of hypertension.

'Inhibace' suppresses the renin-angiotensin-aldosterone system and thereby reduces both supine and standing systolic and diastolic blood pressures. Renin is an enzyme that is released by the kidneys into the circulation to stimulate the production of angiotensin I, an inactive decapeptide. Angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor. Angiotensin II also stimulates aldosterone secretion, leading to sodium and fluid retention. After absorption, cilazapril, a pro-drug, is hydrolyzed to cilazaprilat, the active metabolite, which prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE. Following the administration of 'Inhibace', plasma ACE activity is inhibited more than 90% within two hours at therapeutic doses. Plasma renin activity (PRA) and angiotensin I concentrations are increased and angiotensin II concentrations and aldosterone secretion are decreased.
The increase in PRA comes as a result of the loss of negative feedback on renin release caused by the reduction in angiotensin II.
The decreased aldosterone secretion may lead to small increases in serum potassium along with sodium and fluid loss. In patients with normal renal function, serum potassium usually remains within the normal range during 'Inhibace' treatment. Mean serum potassium values increased by 0.02 mEq/L in patients with a normal baseline serum creatinine and by 0.11 mEq/L in patients with a raised serum creatinine. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise.

ACE is identical to kininase II. Therefore, 'Inhibace' may interfere with the degradation of the vasodepressor peptide bradykinin. The role that this plays in the therapeutic effects of 'Inhibace' is unknown.

The antihypertensive effect of 'Inhibace' is usually apparent within the first hour after administration, with maximum effect observed between three and seven hours after dosing. Supine and standing heart rates remain unchanged. Reflex tachycardia has not been observed. Small, clinically insignificant alterations of heart rate may occur.At recommended doses, the antihypertensive effect of 'Inhibace' is maintained for up to 24 hours. In some patients, blood pressure reduction may diminish toward the end of the dosage interval. Blood pressure should be assessed after two to four weeks of therapy, and dosage adjusted if required. The antihypertensive effect of 'Inhibace' is maintained during long-term therapy. No rapid increase in blood pressure has been observed after abrupt withdrawal of 'Inhibace'.

The blood pressure-lowering effect of 'Inhibace' in black patients may be less pronounced than in non-blacks. Racial differences in response are no longer evident when 'Inhibace' is administered in combination with hydrochlorothiazide.

In hypertensive patients with moderate to severe renal impairment, the glomerular filtration rate and renal blood flow remained in general unchanged with 'Inhibace'.

### Pharmacokinetics

Cilazapril is well absorbed and rapidly converted to the active form, cilazaprilat. Peak plasma concentrations, and times to peak plasma concentrations for cilazapril and cilazaprilat following the oral administration of 0.5 to 5 mg cilazapril are given below:

| Oral | Cilazapril | | Cilazaprilat | |
|---|---|---|---|---|
| Dose (mg) | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $C_{max}$ (ng/mL) | $t_{max}$ (h) |
| 0.5 | 17.0 | 1.1 | 5.4 | 1.8 |
| 1.0 | 33.9 | 1.1 | 12.4 | 1.8 |
| 2.5 | 82.7 | 1.1 | 37.7 | 1.9 |
| 5.0 | 182.0 | 1.0 | 94.2 | 1.6 |

Maximum plasma concentrations of cilazaprilat are reached within two hours after administration of cilazapril.

Maximum ACE inhibition is greater than 90% after 1 to 5 mg cilazapril. Maximum ACE inhibition is 70 to 80% after 0.5 mg cilazapril. Dose proportionality is observed following the administration of 1 to 5 mg cilazapril. Apparent non-proportionality is observed at 0.5 mg reflective of the binding to ACE. The higher doses of cilazapril are associated with longer duration of maximum ACE inhibition.

The absolute bioavailability of cilazaprilat after oral administration of cilazapril is 57% based on urinary recovery data. (The absolute bioavailability of cilazaprilat after oral administration of cilazaprilat is 19%.) Ingestion of food immediately before the administration of cilazapril reduces the average peak plasma concentration of cilazaprilat by 29%, delays the peak by one hour and reduces the bioavailability of cilazaprilat by 14%. These pharmacokinetic changes have little influence on plasma ACE inhibition.

Cilazaprilat is eliminated unchanged by the kidneys. The total urinary recovery of cilazaprilat after intravenous administration of 2.5 mg is 91%. Total clearance is 12.3 L/h and renal clearance is 10.8 L/h. The total urinary recovery of cilazaprilat following the oral administration of 2.5 mg cilazapril is 52.6%.

Half-lives for the periods 1 to 4 hours and 1 to 7 days after the intravenous administration of 2.5 mg cilazaprilat are 0.90 and 46.2 hours respectively. These data suggest the saturable binding of cilazaprilat to ACE. The early elimination phase corresponds to the clearance of free drug. During the terminal elimination phase, almost all of the drug is bound to enzyme. Following the oral administration of 0.5, 1, 2.5 and 5 mg cilazapril, terminal elimination phase half-lives for cilazaprilat are 48.9, 39.8, 38.5 and 35.8 h respectively.

After multiple dose, daily administration of 2.5 mg cilazapril for 8 days, pharmacokinetic parameter values for intact cilazapril after the last dose are similar to the first dose. For cilazaprilat, peak plasma concentrations are achieved at the same time but are 30% higher after the last dose. Trough plasma concentrations and areas under the curve are 20% higher. The terminal elimination phase half-live after the last dose is 53.8 h. The effective half-life of accumulation for cilazaprilat is 8.9 h.

Following the administration of 1 mg cilazapril to healthy elderly and young volunteers, the elderly group experienced greater peak plasma concentrations of cilazaprilat and areas under the curve (39% and 25%, respectively) and lower total clearance and renal clearance (20% and 28%, respectively) than the younger volunteers.

In patients with renal impairment, peak plasma concentrations of cilazaprilat, times to peak plasma concentrations, early elimination phase half-lives, areas under the curve and 24 hour plasma concentrations all increase as creatinine clearance decreases. The changes in these parameters are small for patients with creatinine clearances of 40 mL/min or more. Cilazaprilat clearance (total and renal) decreases in parallel with creatinine clearance. Cilazaprilat is not eliminated in patients with complete renal failure. Hemodialysis reduces concentrations of both cilazapril and cilazaprilat to a limited extent.

Following the administration of 1 mg cilazapril in patients with moderate to severe compensated liver cirrhosis, peak plasma concentrations of cilazapril and cilazaprilat are increased (57% and 28% respectively), attained 30 minutes and 45 minutes earlier, and total clearances are decreased (51% and 31% respectively), in comparison to healthy subjects. The renal clearance and early and terminal elimination phase half-lives of cilazaprilat are decreased 52%, 42% and 62% respectively.

### Indications and clinical use

'Inhibace' (cilazapril) is indicated in the treatment of mild to moderate essential hypertension. 'Inhibace' may be used alone or in combination with thiazide-type diuretics.

In using 'Inhibace' consideration should be given to the risk of angioedema (see WARNINGS).

'Inhibace' should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

'Inhibace' can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of 'Inhibace' in congestive heart failure and renovascular hypertension have not been established and therefore, its use in these conditions is not recommended.

The safety and efficacy of concomitant use of 'Inhibace' with antihypertensive agents other than thiazide diuretics have not been established.

**When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected 'Inhibace' should be discontinued as soon as possible (see WARNINGS; Use in Pregnancy and Information for Patients).**

### Contraindications

'Inhibace' (cilazapril) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

### Warnings

Angioedema: Angioedema has been reported in patients treated with 'Inhibace' (cilazapril). Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, 'Inhibace' should be promptly discontinued and appropriate therapy instituted without delay. The patient should be followed carefully until the swelling has resolved. Swelling confined to the face, lips and mouth usually resolves without treatment, although antihistamines may provide symptomatic relief. Swelling of the tongue, glottis or larynx, may cause airway obstruction, therefore, subcutaneous adrenaline (0.5 mL 1:1000) should be administered promptly when indicated.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at an increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Occasionally, symptomatic hypotension has occurred after administration of 'Inhibace' usually after the first dose or when the dose had been increased. It is more likely to occur in patients with sodium or volume depletion in connection with diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Patients with congestive heart failure, especially those vigorously treated with loop diuretics, may experience excessive hypotension in response to ACE inhibitors. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of 'Inhibace' and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response does not necessitate discontinuation of 'Inhibace'. Once the blood pressure has increased after volume expansion, 'Inhibace' therapy may be continued. If symptoms persist, the dosage should be reduced or the drug discontinued.

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Cases of leucopenia and neutropenia have rarely been reported in patients treated with cilazapril. However, in no patient could a causal relationship to cilazapril be established. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, 'Inhibace' should be discontinued as soon as possible.

In rare cases (probably less than 0.01% of pregnancies) in which no alternative to ACE inhibitors therapy will be found, the mother should be apprised of the potential hazards to their fetuses. Serial ultrasound examinations should be performed to assess fetal development and well-being and the volume of amniotic fluid.

If oligohydramnios is observed, 'Inhibace' should be discontinued unless it is considered life-saving for the mother. A non-stress test (NST), and/or a biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. If concerns regarding fetal well-being still persist, a contraction stress testing (CST) should be considered. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function, however, limited experience with those procedures has not been associated with significant clinical benefit. Dialysis clearance was estimated to be 2.4 L/h for cilazapril and 2.2-2.8 L/h for cilazaprilat.

**Human Data**: It is not known whether exposure limited to the first trimester of pregnancy can adversely affect fetal outcome. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

**Animal Data**: In fertility and general reproduction performance testing in rats, dosing with 50 mg/kg/day of cilazapril resulted in greater implantation losses, less viable fetuses, smaller pups, and dilatation of the renal pelvis in the pups. No teratogenic effects and no adverse effects on postnatal pup development were observed in rats and cynomolgus monkeys during embryotoxicity testing. In the rats, however, at a dose of 400 mg/kg/day, renal cavitation was observed in the pups. In peri- and post-natal toxicity testing in rats, dosing with 50 mg/kg/day resulted in greater pup mortality, smaller pups, and delayed unfolding of the pinna. On administration of $^{14}$C-cilazapril to pregnant mice, rats and monkeys, radioactivity was measured in the fetuses.

### Precautions

Impaired Renal Function: Renal function should be assessed in all patients with suspected renal impairment before initiating therapy with 'Inhibace'(cilazapril).

'Inhibace' should be used with caution in patients with renal impairment as they may require reduced or less frequent doses dependent upon their creatinine clearance (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter as a consequence of treatment with 'Inhibace', or may improve.

In patients with severe heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including 'Inhibace', may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

Increases in blood urea nitrogen and/or serum creatinine have been observed in hypertensive patients with unilateral or bilateral renal artery stenosis treated with 'Inhibace'. These increases are usually reversible upon discontinuation of 'Inhibace' and/or diuretic therapy. In such patients, renal function should be closely monitored.

Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when cilazapril has been given concurrently with a diuretic. Dosage reduction and/or discontinuation of the diuretic and/or cilazapril may be required.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: In clinical trials, elevated serum potassium (greater than 5.5 mEq/L) was observed in approximately 0.7% of hypertensive patients receiving cilazapril. In most cases these were isolated values which resolved despite continued therapy, however in one case the patient discontinued treatment. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (see Drug Interactions and ADVERSE REACTIONS).

Valvular Stenosis: There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, cilazapril blocks angiotensin II formation, secondary to compensatory renin release. This may result in arterial hypotension which can be corrected by volume expansion.

Patients With Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), jaundice, elevations of liver enzymes and/or serum bilirubin have occurred during therapy with other ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported for 'Inhibace' (see ADVERSE REACTIONS). Jaundice was also spontaneously reported in one patient worldwide. Should the patient receiving 'Inhibace' experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of 'Inhibace' should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. 'Inhibace' should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of 'Inhibace', has been reported. Such possibility should be considered as part of the differential diagnosis of the cough.

Nursing Mothers: In rats, it has been shown that after the oral administration of cilazapril, cilazaprilat is excreted in milk.

It is not known whether cilazapril and/or cilazaprilat are excreted in human breast milk. Caution should be exercised when cilazapril is administered to nursing mothers.

Pediatric Use: The safety and effectiveness of the use of 'Inhibace' in children have not been established. Therefore, use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out (see ACTIONS AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**Drug Interactions**

Diuretic Therapy: Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of hypotensive effects after the first dose of 'Inhibace' can be minimized by either discontinuing the diuretic, or increasing the salt intake prior to initiation of treatment with 'Inhibace'. If it is not possible to discontinue the diuretic, the starting dose of 'Inhibace' should be reduced and the patient should be closely observed for several hours following initial dose and until blood pressure has stabilized (see WARNINGS and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium: Since cilazapril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution since they may lead to a significant increase in serum potassium. Salt substitutes containing potassium should also be used with caution.

Agents Causing Renin Release: The antihypertensive effect of 'Inhibace' is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Agents Affecting Sympathetic Activity: Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs may add some further antihypertensive effect to cilazapril.

Inhibitors of Endogenous Prostaglandin Synthesis: Concomitant administration of a non-steroidal anti-inflammatory drug (NSAID) may reduce the antihypertensive effect of 'Inhibace'. The introduction of therapy with cilazapril (2.5 mg once daily) in hypertensive patients receiving indomethacin (50 mg twice daily) did not result in a reduction in blood pressure. However, the introduction of therapy with indomethacin (50 mg twice daily) in hypertensive patients receiving cilazapril (2.5 mg once daily) did not attenuate the blood pressure lowering effects of cilazapril. The interaction does not appear to occur in patients treated with 'Inhibace' prior to the administration of a NSAID. There was no evidence of a pharmacokinetic interaction between cilazapril and indomethacin.

Digoxin: No pharmacodynamic or pharmacokinetic interactions (and no increase in plasma digoxin concentrations) were observed when cilazapril therapy (5 mg once daily) was administered to healthy volunteers receiving digoxin (0.25 mg twice daily).

Lithium Salts: As with other drugs which eliminate sodium, lithium elimination may be reduced. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered.

**Adverse Reactions**

'Inhibace' (cilazapril) has been evaluated for safety in 5450 patients treated for essential hypertension. Of these 2586 participated in controlled clinical trials. 'Inhibace' was evaluated for long-term safety in approximately 798 hypertensive patients treated for one year or longer.

The most frequent adverse reactions ($\geq$ 1%) reported in controlled clinical trials were: headache (5.1%), dizziness (3.0%), fatigue (2.1%), cough (1.8%) and nausea (1.3%). Discontinuation of therapy was required in 63 (2.4%) patients.

The most severe adverse reactions reported in the 5450 patients treated with 'Inhibace' included: angioedema/face edema (0.1%), postural hypotension (0.3%), orthostatic hypotension (2.1%), myocardial infarction (0.1%), cerebrovascular disorder (0.04%), renal failure (0.09%), and thrombocytopenic purpura (0.02%).

Adverse reactions occurring in less than 1% of the 5450 patients treated with 'Inhibace' in controlled and uncontrolled clinical trials were:
**Cardiovascular**: Chest Pain, palpitations, postural hypotension, flushing, tachycardia, angina pectoris.
Syncope, atrial fibrillation, arrhythmia, hypotension (not postural), myocardial infarction: reported in 0.1% or less of the patients.

**Renal**: Micturition frequency.
Polyuria, dysuria, renal failure, renal pain: reported in 0.1% or less of the patients.

**Hematologic**: Epistaxis.
Anemia, purpura: reported in 0.1% or less of the patients.

**Gastrointestinal**: Dyspepsia, abdominal pain, diarrhea, constipation, vomiting, flatulence.
Anorexia, GI bleeding, rectum bleeding: reported in 0.1% or less of the patients.

**Dermatologic/Allergic**: Rash (includes maculo-papular rash and erythematous rash), pruritus.
Urticaria, angioedema (including face edema), dermatitis: reported in 0.1% of the patients.

**Nervous System**: Somnolence, increased sweating, paresthesia, impotence, depression, anxiety, dry mouth, insomnia, hypoesthesia, vertigo.
Migraine, tremor, dysphonia, nervousness, ataxia, confusion, decreased libido: reported in 0.1% or less of the patients.

**Musculoskeletal**: Myalgia, leg cramps, arthralgia.

**Special Senses**: Tinnitus, abnormal vision.
Taste perversion, photophobia: reported in less than 0.1% of the patients.

**Respiratory**: Rhinitis, dyspnea, pharyngitis, bronchospasm.
Respiratory tract infection, sinusitis, bronchitis: reported in 0.1% or less of the patients.

**Metabolic**: Gout: reported in less than 0.1% of the patients.

**Body as a Whole**: Asthenia, malaise, hot flushes, pain, conjunctivitis, edema. Rigors: reported in less than 0.1% of the patients.

**Abnormal Laboratory Findings**

**Hematology**: Patients had clinically relevant changes in platelet (0.4%), neutrophil (1.9%) or white blood cell counts (1.3%).
**Leucopenia and neutropenia**: Leucopenia was observed in 0.2% (10/3,580) and neutropenia in 0.4% (22/5,720) of the patients. Most of these were single, transient occurrences; one case with two successive abnormalities showed no associated clinical symptoms.

**Liver Function Tests**: Clinically relevant changes in the values associated with liver function (SGOT, SGPT, GGTP, LDH, total bilirubin and alkaline phosphatase) occurred in 0.1% (bilirubin) to 1.1% (SGPT, GGTP) of the patients. Most of these abnormalities were transient.

**Renal**: Clinically relevant changes in renal function test results (BUN or serum creatinine concentrations) occurred in 0.6% or less of the patients.
**Hyperkalemia**: (see PRECAUTIONS)
**Creatinine**: Serum creatinine values > 2 mg/dL were reported in 1.3% (44/3,468) of the patients. Two thirds of these patients had renal impairment at baseline.
**Proteinuria** ($\geq$2+ dipstick reaction or excretion of $\geq$ 1 g/24h): Proteinuria considered remotely, possibly or probably related to therapy was reported in 0.5% (17/3,421) of the patients. Five patients had prior renal impairment.

**Symptoms and Treatment of Overdosage**

Limited data are available with regard to overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should be normally treated by intravenous volume expansion with normal saline.

Hemodialysis removes cilazapril and cilazaprilat from the general circulation to a limited extent.

**Dosage and Administration**

Dosage of 'Inhibace' (cilazapril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents being used with 'Inhibace' may need to be adjusted.

The dose should always be taken at about the same time each day.

**Monotherapy**: The recommended initial dose of 'Inhibace' is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range for 'Inhibace' is 2.5 to 5 mg once daily. Minimal additional blood pressure lowering effects were achieved with a dose of 10 mg once daily. A dose of 10 mg should not be exceeded.

In most patients, the antihypertensive effect of 'Inhibace' is maintained with a once a day dosing regimen. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not adequately controlled with 'Inhibace' alone a non-potassium-sparing diuretic may be administered concomitantly. After the addition of a diuretic, it may be possible to reduce the dose of 'Inhibace'.

Concomitant Diuretic Therapy: in patients receiving diuretics, 'Inhibace' therapy should be initiated with caution, since they are usually volume depleted and more likely to experience hypotension following ACE inhibition. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of 'Inhibace' to reduce the likelihood of hypotension (see WARNINGS). If this is not possible because of the patient's condition, 'Inhibace' should be started at 0.5 mg once daily and the blood pressure closely monitored after the first dose until stabilized. Thereafter, the dose should be adjusted according to individual response.

Dosage in Elderly Patients (Over 65 Years): 'Inhibace' treatment should be initiated with 1.25 mg (half of a 2.5 mg tablet) once daily or less, depending on the patient's volume status and general condition. Thereafter, the dose of 'Inhibace' must be adjusted according to individual response.

Dosage Adjustment in Renal Impairment: The following dose schedules are recommended:

| Creatinine Clearance | Initial Dose of 'Inhibace' | Maximal Dose of 'Inhibace' |
|---|---|---|
| > 40 mL/min | 1 mg once daily | 5 mg once daily |
| 10-40 mL/min | 0.5 mg once daily | 2.5 mg once daily |
| < 10 mL/min | 0.25-0.5 mg once or twice a week according to blood pressure response | |

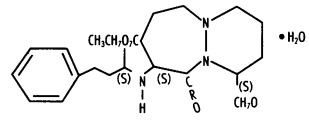
Hemodialysis patients: 'Inhibace' should be administered on days when dialysis is not performed and the dosage should be adjusted according to blood pressure response.

Dosage Adjustment in Hepatic Impairment: Should patients with liver cirrhosis require treatment with 'Inhibace', treatment should be initiated with caution at a dose of 0.5 mg once daily or less as significant hypotension may occur (see PRECAUTIONS).

**Pharmaceutical Information**

Drug Substance:
Proper Name: cilazapril monohydrate
Chemical Name: 9(s)-[1(s)-(ethoxycarbonyl)-3-phenylpropylamino]-octahydro-10-oxo-6H-pyridazo [1,2-a] [1,2] diazepine-1(s)-carboxylic acid monohydrate

Structural Formula:




Molecular Formula: $C_{22}H_{31}N_3O_5 \bullet H_2O$
Molecular Weight: 435.52
Physical Form: White to off-white crystalline powder
Solubility: Water (25°C) 0.5 g/100 mL
$pka_1$, $pka_2$: 3.3, 6.4
pH (1% suspension): 4.9
Partition Coefficient: 0.8 (octanol-pH 7.4 buffer 22°C)
Melting Point: 98°C with decomposition

Composition: 'Inhibace' 1 mg, 2.5 mg and 5 mg film-coated tablets contain 1 mg, 2.5 mg and 5 mg cilazapril, as cilazapril monohydrate, respectively. Non-medicinal ingredients: the tablets also contain lactose, cornstarch, hydroxypropyl methylcellulose, talc, sodium stearyl fumarate and titanium dioxide. In addition, iron oxide is present in the 1 mg, 2.5 mg and 5 mg tablets.

Stability and Storage Recommendations: Store 15-30°C. Keep container tightly closed.

**Availability of Dosage Forms**

'Inhibace' (cilazapril) is available in film-coated tablets containing:
1 mg cilazapril - yellow, oval shaped, single scored biconvex tablets, imprinted ROCHE 1. Available in bottles of 100 tablets.
2.5 mg cilazapril - pinkish-brown, oval shaped, single scored biconvex tablets, imprinted ROCHE 2.5. Available in bottles of 100 tablets.
5 mg cilazapril - reddish-brown, oval shaped, single scored biconvex tablets, imprinted ROCHE 5. Available in bottles of 100 tablets.

**References** 1) 'Inhibace' Product Monograph
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4) Deng LY and Schiffrin EL, J Cardiovasc Pharmacol, 1993, in press
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PRODUCT MONOGRAPH AVAILABLE UPON REQUEST
DATE OF PREPARATION: March 16, 1993



PAAB

Roche

NEW ONCE-A-DAY

cilazapril

℞ INHIBACE™

Fight the Effects of Angiotensin II & Hypertension

# TRIPHASIL®

(levonorgestrel and ethinyl estradiol tablets USP)

## Prescribing Information

**INDICATION:** Conception control

**CONTRAINDICATIONS:** 1. Thrombophlebitis, thromboembolic disorders, or a history of these conditions. 2. Cerebrovascular disorders. 3. Myocardial infarction. 4. Active liver disease. 5. History of cholestatic jaundice. 6. Known or suspected carcinoma of the breast. 7. Known or suspected estrogen-dependent neoplasia. 8. Undiagnosed abnormal vaginal bleeding. 9. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields. 10. When pregnancy is suspected or diagnosed.

**WARNINGS:** 1. **Predisposing Factors For Coronary Artery Diseases:** In women with predisposing factors for coronary artery disease (such as cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, and increasing age) oral contraceptives have been reported as an additional risk factor. **After the age of 35 years, for purposes of fertility control, oral contraceptives should be considered only in exceptional circumstances and when the risk/benefit ratio has been carefully weighed by both the patient and the physician.**

> Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and heavy smoking (15 or more cigarettes per day) and is more marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Estrogen-progestogen combinations may cause an increase in plasma lipoproteins and should be administered with caution to women known to have pre-existent hyperlipoproteinemia. Lipid profiles should be determined regularly in these patients. The combination of obesity, hypertension, and diabetes is particularly hazardous to women who are taking oral contraceptives. Should this triad of conditions develop, the patient should be placed on an alternate method of contraception. 2. Discontinue medication at the earliest manifestation of: A. **Thromboembolic and Cardiovascular Disorders** such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis. The use of estrogen-progestogen combination oral contraceptives should be avoided in conditions which predispose to venous stasis and to vascular thrombosis, e.g., immobilization after accidents or confinement to bed during long-term illness. Under such conditions, other non-hormonal methods of contraception should be considered. For use of oral contraceptives when surgery is contemplated, see PRECAUTIONS. B. **Visual Defects, Partial or Complete.** C. **Papilledema, or Ophthalmic Vascular Lesions.** D. **Severe Headache of Unknown Etiology.** 3. Fetal abnormalities have been reported to occur in the offspring of women who have taken estrogen-progestogen combinations in early pregnancy. Rule out pregnancy as soon as it is suspected. 4. The use of oral contraceptives during the period a mother is breastfeeding her infant may not be advisable. The hormonal components are excreted in breast milk and may reduce its quantity and quality. The long-term effects of the developing child are not known. 5. This drug may cause fluid retention. Conditions such as epilepsy, asthma, and cardiac or renal dysfunction require careful observation.

**PRECAUTIONS:** 1. **Physical Examination and Follow-up:** Before oral contraceptives are used, a thorough history and physical examination should be made including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active and a urinalysis should be done. The first follow-up examination should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be made at least once a year, more frequently for those patients at greater risk for adverse effects. At each annual visit, examination should include those procedures outlined above that were done at the initial visit. 2. **Hepatic Function:** Patients who have had jaundice should be given oral contraceptives with great care and under close observation. If there is a clear-cut history of cholestatic jaundice, especially if it occurred during pregnancy, other methods of contraception should be prescribed. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If the jaundice should prove to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported. Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are uncommon, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding. 3. **Hypertension:** Patients with essential hypertension whose blood pressure is well-controlled may be given the drug but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary. 4. **Migraine and Headache:** The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 5. **Diabetes:** Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any alterations in carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be closely observed. 6. **Metabolic and Endocrine Diseases:** In metabolic or endocrine diseases and when metabolism of calcium and phosphorus is abnormal, careful clinical evaluation should precede medication and a regular follow-up is recommended. 7. **Ocular Disease:** Progressive astigmatic error, possibly leading to keratoconus, has been noted in some myopic women receiving oral contraceptives. In women who developed myopia at or near puberty, and in whom myopia stabilized in adult life, oral contraceptives after some 6 months of use have increased the refractive error 2- to 3-fold. Women with a family history of myopic astigmatism or keratoconus who are using oral contraceptives may experience rapid advancement of the ocular disorder. **Contact lens wearers** who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist and temporary or permanent cessation of wear considered. 8. **Connective Tissue Disease:** The use of oral contraceptives in some women has been associated with positive lupus erythematous cell tests and with clinical lupus erythematosus. In some instances exacerbation of rheumatoid arthritis and synovitis have been observed. 9. **Breasts:** Although oral contraceptive use has not been shown to increase the risk of developing breast cancer, particular attention should be paid to women who have an immediate family history of this disease and are therefore more prone to its development. Careful monitoring is mandatory because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression if the malignancy is hormone-dependent. Special judgement should be used in prescribing oral contraceptives for women with fibrocystic disease of the breast. Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. 10. **Vaginal Bleeding:** Persistent irregular vaginal bleeding requires special diagnostic judgement to exclude the possibility of pregnancy or neoplasm. If these can be excluded, prescribing a product containing a higher dosage of estrogen may correct the problem. 11. **Fibroids:** Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuance of medication. 12. **Age:** In general, women in the later reproductive years gradually assume an increasing risk of circulatory and metabolic complications which becomes more prominent at 35 years of age. In view of this, closer observation, shorter duration of oral contraceptive use, and avoidance of cigarette smoking is advisable. Alternatively, adoption of other means of birth control should be considered for this age group. Oral contraceptives may mask the onset of the climacteric. 13. **Emotional Disorders:** Patients with a history of emotional disturbances, especially the depressive type, are more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship. 14. **Laboratory Tests:** Laboratory test results should not be considered reliable unless oral contraceptive therapy has been discontinued for 2 to 4 months because therapy may alter the following determinations and possibly mask underlying disease: A. **Liver function tests:** Bromsulphalein retention – increased. SGOT – variously reported elevations. Alkaline phosphatase and gamma GT – slightly elevated. B. **Coagulation tests:** Evaluation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X. Increased platelet aggregation. Decreased antithrombin III. C. **Thyroid function tests:** Protein binding of thyroxine is increased as indicated by increased PBI and total serum thyroxine concentrations and decreased $T_3$ resin uptake. D. **Adrenocortical function tests:** Plasma cortisol is increased. Reported impaired adrenocortical response is now attributed to accelerated metapyrone conjugation by estrogen. E. **Reproductive endocrine profile changes:** Luteinizing hormone – the mid-cycle surge is suppressed. Pregnanediol – suppressed. Serum prolactin – may be elevated. F. **Other tests: Increase in:** phospholipids and triglycerides; cryofibrinogen; ceruloplasmin; cholinesterase; haptoglobulins; transferrin; plasminogen; alpha-2-macroglobulin; testosterone binding globulin; estrogen binding globulin; angiotensinogen; aldosterone secretion rate; serum magnesium, copper, or zinc; iron binding capacity. **Decrease in:** orosomucoid; serum folate; serum cyanocobolamin; serum pyridoxine (disturbed tryptophan metabolism); glucose tolerance (temporary). **Variable changes:** Lipoprotein cholesterol fractions: The clinical relevance of those alterations that have been reported to be statistically significant has yet to be demonstrated. 15. **Tissue Specimens:** Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures are submitted for examination. 16. **Return to Fertility:** After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred. An alternate contraceptive method should be used during this time. 17. **Amenorrhea:** Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following estrogen-progestogen combination therapy. Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function. 18. **Thromboembolic Complications – Post-Surgery:** Retrospective studies have reported an increased risk of post-surgery thromboembolic complications in oral contraceptive users. If feasible, oral contraceptives should be discontinued and a non-hormonal method substituted at least one month prior to elective major surgery. Oral contraceptives should not be resumed until at least two weeks after hospital discharge following surgery. 19. **Drug Interactions:** A. Concurrent use of the following drugs may result in reduced contraceptive reliability and increased incidence of breakthrough bleeding: ampicillin; analgesics; antimigraine preparations; chloramphenicol; isoniazid; neomycin; nitrofurantoin; penicillin V; phenylbutazone; sulfonamides; tetracycline. B. Concurrent use of anticoagulants with oral contraceptives may reduce the anticoagulant effect. C. Effectiveness of the following drugs may be altered when used concurrently with oral contraceptives: antihypertensives; hypoglycemics; tricyclic antidepressants; vitamins. D. Concurrent use of the following drugs may reduce contraceptive reliability because of accelerated estrogen metabolism caused by the induction of hepatic enzymes: carbamazepine; phenobarbital; phenytoin; primidone; rifampicin.

**ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives: thrombophlebitis; pulmonary embolism; mesenteric thrombosis; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; myocardial infarction; cerebral thrombosis; cerebral hemorrhage; hypertension; benign hepatic tumors; gallbladder disease; congenital anomalies. The following adverse reactions also have been reported in patients receiving oral contraceptives: Nausea and vomiting, usually the most common adverse reaction occurring in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); endocervical hyperplasias; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; premenstrual-like syndrome; intolerance to contact lenses; change in corneal curvature (steepening); cataracts; optic neuritis; retinal thrombosis; changes in libido; chorea; changes in appetite; cystitis-like syndrome; rhinitis; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired renal function; Raynaud's phenomenon; auditory disturbances; hemolytic uremic syndrome; pancreatitis.

**DOSAGE:** Triphasil – 21-day regimen. For the first cycle of medication, the patient is instructed to take one tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle. The tablets are then discontinued for seven days (one week). Triphasil – 28-day regimen. For the first cycle of medication, the patient is instructed to take one tablet daily for 28 consecutive days beginning on Day 1 of her menstrual cycle.

**AVAILABILITY:** Triphasil tablets are available in 21-day regimen and 28-day regimen Cyclette® packages. Each Cyclette contains three different microgram dose combinations of levonorgestrel and ethinyl estradiol in the following manner: Days 1–6: Each pale brown tablet contains 50 $\mu$g levonorgestrel plus 30 $\mu$g ethinyl estradiol. Days 7–11: Each white tablet contains 75 $\mu$g levonorgestrel plus 40 $\mu$g ethinyl estradiol. Days 12–21: Each yellow tablet contains 125 $\mu$g levonorgestrel plus 30 $\mu$g ethinyl estradiol. In the 28-day regimen package, each green tablet taken on days 22–28 contains inert ingredients. Product Monograph is available to physicians and pharmacists on request. Copies of the Supplementary Information for patients considering the use of oral contraceptives are available from Wyeth representatives.

**REFERENCES:**


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3. Lemay A, Dewailly SD, Grenier R, et al: Attenuation of mild hyperandrogenic activity in postpubertal acne by a triphasic oral contraceptive containing low doses of ethynyl estradiol and d,l-norgestrel. *J Clin Endocrinol Metab* 1990;71:8-14.
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6. Schilling LH, Bolding OT, Chenault CB, et al: Evaluation of the clinical performance of three triphasic oral contraceptives: A multicenter, randomized comparative trial. *Am J Obstet Gynecol* 1988; 160(suppl): 1264-1268.
7. Upton GV: Clinical experience with the triphasic oral contraceptive, in Elstein M(ed): *Update on Triphasic Oral Contraception*. Princeton, NJ, Excerpta Medica, 1983, pp 54-74.



WYETH-AYERST CANADA INC.
Montreal, Canada H4R 1J6

TRI-EJ-07/93

PAAB CCPP

Once-a-day

# Pr CARDIZEM® CD

Controlled Delivery diltiazem HCl/NORDIC

# PRESCRIBING INFORMATION

Pr CARDIZEM® CD Once-a-day Controlled Delivery Capsules
120 mg, 180 mg, 240 mg and 300 mg

## THERAPEUTIC CLASSIFICATION

Antihypertensive and Antianginal agent.

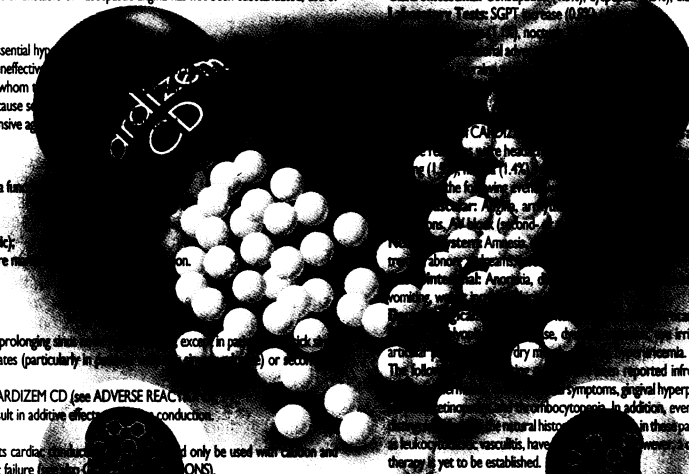
## INDICATIONS AND CLINICAL USE

### Angina

1. CARDIZEM CD is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.
2. CARDIZEM CD may be tried in combination with beta-blockers in chronic stable angina patients with normal ventricular function. When such concomitant therapy is introduced, patients must be monitored closely (See WARNINGS).
3. Since the safety and efficacy of CD capsules in the management of unstable or vasospastic angina has not been substantiated, use of this formulation for these indications is not recommended.

### Hypertension

CARDIZEM CD is indicated for the treatment of mild to moderate essential hyp
patients in whom treatment with diuretics or beta-blockers has been ineffecti
CARDIZEM CD can be tried as an initial agent in those patients in whom t
in patients with medical conditions in which these drugs frequently cause s
Safety of concurrent use of CARDIZEM CD with other antihypertensive a




## CONTRAINDICATIONS

Diltiazem HCl is contraindicated:

1. In patients with sick sinus syndrome except in the presence of a fun
2. In patients with second or third degree AV block;
3. In patients with known hypersensitivity to diltiazem;
4. In patients with severe hypotension (less than 90 mm Hg systolic);
5. In myocardial infarction patients, who have left ventricular failure m on.
6. In pregnancy and in women of child-bearing potential.

## WARNINGS

### Cardiac Conduction

Diltiazem prolongs AV node refractory periods without significantly prolonging sin (exce in p or
syndrome. This effect may rarely result in abnormally slow heart rates (particularly in
third-degree AV block (6 of 1208 patients or 0.5%).
First degree AV block was observed in 5.8% of patients receiving CARDIZEM CD (see ADVERSE REAC
Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effect conduction

### Congestive Heart Failure

Because diltiazem has a negative inotropic effect *in vitro* and it affects cardia d only be used with caution and
under careful medical supervision in patients with congestive cardiac failure ( ONS).

### Use with Beta-blockers

The combination of diltiazem and beta-blockers warrants caution since in some on heart rate, AV conduction, blood
pressure or left ventricular function have been observed. Close medical supervis
Generally, diltiazem should not be given to patients with impaired left ventricular fun y receive beta-blockers. However, in
exceptional cases when, in the opinion of the physician, concomitant use is considered essential, such use should be instituted gradually in
a hospital setting.
Diltiazem gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual
reduction of the dose of beta-blocker.

### Hypotension

Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension.
In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of diltiazem should be taken into
consideration.

### Acute Hepatic Injury

In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury
have been observed. These reactions have been reversible upon discontinuation of drug therapy. Although a causal relationship to diltiazem
has not been established in all cases, a drug induced hypersensitivity reaction is suspected (see ADVERSE REACTIONS). As with any drug
given over prolonged periods, laboratory parameters should be monitored at regular intervals.

## PRECAUTIONS

### Impaired Hepatic or Renal Function

Because diltiazem is extensively metabolized by the liver and excreted by the kidney and in bile, monitoring of laboratory parameters and
cautious dosage titration are recommended in patients with impaired hepatic or renal function (see ADVERSE REACTIONS).

### Pediatric Use

The safety of diltiazem in children has not yet been established.

### Nursing Mothers

Diltiazem has been reported to be excreted in human milk. One report suggests that concentrations in breast milk may approximate serum
levels. Since diltiazem safety in newborns has not been established, it should not be given to nursing mothers.

### Use in the Elderly

Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. The incidence of adverse reactions is
approximately 13% higher in this group. Those adverse reactions which occur more frequently include: peripheral edema, bradycardia,
palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable (see DOSAGE AND ADMINISTRATION).

### Drug Interactions

**Digitalis:** Diltiazem and digitalis glycosides may have an additive effect in prolonging AV conduction. In clinical trials, concurrent
administration of diltiazem and digoxin have resulted in increases in serum digoxin levels with prolongation of AV conduction. This increase
may result from a decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should
be carefully monitored. The dose of digoxin may need downward adjustment.
**Beta-blockers:** The concomitant administration of diltiazem with beta adrenergic blocking drugs warrants caution and careful monitoring.
Such an association may have an additive effect on heart rate, on AV conduction or on blood pressure. (See WARNINGS.) Appropriate
dosage adjustments may be necessary. A study in five normal subjects showed that diltiazem increased propranolol bioavailability by
approximately 50%.
**Short and Long-acting Nitrates:** Diltiazem may be safely co-administered with nitrates, but there have been few controlled studies to
evaluate the antianginal effectiveness of this combination.
**Other Calcium Antagonists:** Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil
or to nifedipine, using diltiazem in conjunction with either of these drugs may be beneficial.

## ADVERSE REACTIONS

### Angina

The safety of CARDIZEM CD, administered at doses up to 360 mg a day, was evaluated in 365 patients with chronic stable angina treated
in controlled and open-label clinical trials. Adverse events were reported in 21.1% of patients, and required discontinuation in 2.2% of
patients. The most common adverse effects reported were: first degree AV block (5.8%), dizziness (3.0%), headache (3.0%), asthenia (2.7%).
bradycardia (2.5%), and angina pectoris (1.6%).
The following percentage of adverse effects, divided by system, was reported:
**Cardiovascular:** First degree AV block (5.8%), bradycardia (2.5%), angina pectoris (1.6%), peripheral edema (1.4%), palpitations (1.1%),
and ventricular extrasystoles (0.8%).
**Central Nervous System:** Dizziness (3.0%), headache (3.0%), asthenia (2.7%), insomnia (1.1%), nervousness (0.8%).
**Gastrointestinal:** Nausea (1.4%), diarrhea (0.5%).
**Dermatological:** Rash (0.8%)
**Other:** Amblyopia (0.5%)

The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: bundle branch block, ventricular
tachycardia, ECG abnormality, supraventricular extrasystoles, chest pain, syncope, postural hypotension, paresthesia, tremor, depression,
mental confusion, impotence, abdominal pain, constipation, GI disorder, epistaxis, nuchalrigidity, myalgia.
**Hypertension:** A safety evaluation was carried out in controlled studies in 378 hypertensive patients treated with CARDIZEM CD at
doses up to 360 mg a day. Adverse effects were reported in 30.7% of patients and required discontinuation of therapy in 2.1%. The most
common adverse effects were: headache (8.7%); edema (4.0%); bradycardia (3.7%); dizziness (3.4%), ECG abnormality (2.9%); asthenia (2.6%)
and first degree AV block (2.1%).
The following percentage of adverse effects, divided by system, was reported:
**Cardiovascular:** Edema peripheral (4.0%), bradycardia (3.7%), ECG abnormalities (2.9%), first degree AV block (2.1%), arrhythmia (1.6%),
vasodilation (flushing) (1.6%), bundle branch block (0.8%), cardiomegaly (0.5%), hypotension (0.5%).
**Central Nervous System:** Headache (8.7%), dizziness (3.4%), asthenia (2.6%), somnolence (1.3%), nervousness (1.1%).
**Gastrointestinal:** Constipation (1.3%), dyspepsia (1.3%), diarrhea (0.6%).
**Laboratory Tests:** SGPT, alkalase (0.8%)

ncidence of less than 0.5% in clinical trials: systolic murmur, supraventricular
n weight, albuminuria, bilirubinemia, hyperuricemia, thirst, insomnia, vertigo,
, tinnitus, and elevations in creatine kinase, alkaline phosphatase, and SGOT.

and CARDIZEM CD capsules involving over 3300 patients, the most common
s (3.5%), asthenia (2.7%), first-degree AV block (2.4%), bradycardia (1.7%),

less than 1.0%.
cardia, ventricular extrasystoles, congestive heart failure, syncope,
abnormalities.
s, somnolence, hallucinations, paresthesia, personality change, tinnitus,

e of SGOT, SGPT, LDH, and alkaline phosphatase (see WARNINGS),

ria.
irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteo-
cemia.
eported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme,
symptoms, gingival hyperplasia, hemolytic anemia, detached retina, increased bleeding time, leukopenia,
thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily
natural history in these patients. A number of well-documented cases of generalized rash, characterized
vasculitis, have definitive cause and effect relationship between these events and CARDIZEM
therapy is yet to be established.

## SYMPTOMS AND TR ERDOSAGE

Overdosage with oral diltiazem has . Eight (8) patients recovered without sequelae over a few days. One patient
who had ingested an unknown amount of mide and alcohol experienced a fatal cardiac arrest. Doses ingested ranged from
1.8 to 10.8 grams. Bradycardia, AV block sion were noted in most patients.
In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage.
The following measures may be considered:

### Bradycardia

Administer atropine. If there is no response to vagal blockade, administer isoproterenol cautiously.

### High Degree AV Block

Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing.

### Cardiac Failure

Administer inotropic agents (isoproterenol, dopamine or dobutamine) and diuretics.

### Hypotension

Vasopressors (e.g., dopamine or levarterenol bitartrate).
Actual treatment and dosage should depend on the severity of the clinical situation.

## DOSAGE AND ADMINISTRATION

### Angina

Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual
patients may respond to higher doses of up to 360 mg once daily. When necessary, titration should be carried out over a 7 to 14 day period.
Patients controlled on diltiazem alone or in combination with other medications may be safely switched to CARDIZEM CD capsules at the
nearest equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically
warranted. There is limited experience with doses above 360 mg, however, the incidence of adverse reactions increases as the dose increases
with first degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose. Therefore, doses greater than
360 mg are not recommended.

### Hypertension

Dosage should be individualized depending on patient's tolerance and responsiveness to CARDIZEM CD capsules.
When used as monotherapy, usual starting doses are 180 to 240 mg once daily, although some patients may respond to 120 mg once daily.
Maximum antihypertensive effect is usually observed after approximately 2 to 4 weeks of therapy; therefore, dosage adjustments should be
scheduled accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg once daily.
A maximum daily dose of 360 mg once daily should not be exceeded.
The dosage of CARDIZEM CD or concomitant antihypertensive agents may need to be adjusted when adding one to the other. See
WARNINGS and PRECAUTIONS regarding use with beta-blockers.
Hypertensive patients controlled on CARDIZEM SR alone or in combination with other antihypertensive agents may be safely switched to
CARDIZEM CD at the same total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as
clinically warranted.
CARDIZEM CD capsules should not be chewed or crushed.

## AVAILABILITY

CARDIZEM CD 120 mg capsules are supplied in bottles of 100. Each light turquoise blue capsule is imprinted with CARDIZEM CD
120 mg.
CARDIZEM CD 180 mg capsules are supplied in bottles of 100. Each light blue/light turquoise blue capsule is imprinted with CARDIZEM CD
180 mg.
CARDIZEM CD 240 mg capsules are supplied in bottles of 100. Each light blue/light blue capsule is imprinted with CARDIZEM CD 240 mg.
CARDIZEM CD 300 mg capsules are supplied in bottles of 100. Each light blue/light gray capsule is imprinted with CARDIZEM CD 300 mg.

Product Monograph available on request.
®Cardizem is a registered trademark of Marion Merrell Dow Inc., U.S.A.

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Subsidiary of Marion Merrell Dow Canada

# LESCOL*

FLUVASTATIN SODIUM

## PRESCRIBING INFORMATION

20 mg and 40 mg capsules

**THERAPEUTIC CLASSIFICATION** – Lipid metabolism regulator

**ACTIONS AND CLINICAL PHARMACOLOGY** – LESCOL* (fluvastatin sodium) is a synthetic HMG-CoA reductase inhibitor, and is hydrophillic. Fluvastatin sodium is a racemate of two erythro enantiomers of which one exerts the pharmacological activity. LESCOL is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma total cholesterol (total-C) and low density lipoprotein cholesterol (LDL-C) concentrations.

**INDICATIONS AND CLINICAL USE** – The primary therapeutic indication for LESCOL (fluvastatin sodium) is as an adjunct to diet (at least equivalent to the American Heart Association [AHA] Step 1 Diet) in the treatment of elevated total cholesterol (total-C) and LDL-C levels in patients with primary hypercholesterolemia (Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate. Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of LESCOL, a lipid profile should be performed to measure total-C, HDL-C and TG. For patients with TG < 4.52 mmol/L (< 400 mg/dL), LDL-C can be estimated using the following equation: LDL-C (mmol/L) = total-C - HDL-C - 0.37 TG. For TG levels > 4.52 mmol/L (> 400 mg/dL), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, as with other HMG-CoA reductase inhibitors, LESCOL is not indicated. Since the goal of treatment is to lower LDL-C, LDL-C levels should be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy. LESCOL has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e. hyperlipoproteinemia Types I, III, IV, or V).

**CONTRAINDICATIONS** – Hypersensitivity to any component of this medication. LESCOL (fluvastatin sodium) is contraindicated in patients with active liver disease or unexplained, persistent clinically relevant elevations in serum transaminases (see WARNINGS). As with other drugs of this class, LESCOL is contraindicated during pregnancy and in nursing mothers (see PRECAUTIONS).

**WARNINGS – As for other drugs of this class, the effect of fluvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality, or total mortality has not been established. Liver Enzymes:** Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. A small number of patients treated with LESCOL (fluvastatin sodium) in controlled trials (n = 17 of 1524; 1.1%) developed marked persistent elevations (to more than 3 times the upper limit of normal) of transaminase levels. Most of these abnormalities occurred within the first 6 weeks of treatment (time of occurrence ranging from 2 to 54 weeks). In patients in which the drug was discontinued (10/17), the transaminases levels usually declined rapidly to pretreatment levels. Two patients in which therapy was not interrupted, had transaminases elevations possibly related to the study drug; these abnormalities slowly resolved on continued therapy. In a long-term open label extension study, 5 of 824 (0.6%) patients exposed to LESCOL at a dose of 40 mg/day developed persistent transaminase elevations. Only two of these patients were discontinued from the study. The majority of these abnormal biochemical findings were asymptomatic. **It is recommended that liver function tests be performed within the first 12 weeks after initiation of treatment or after an increase in the dose, and periodically thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with LESCOL. Any patient on LESCOL complaining of flu-like symptoms, malaise, fatigue should be evaluated clinically and, if warranted, should have serum transaminases measured as these may be common presenting symptoms of serious liver damage. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. **Should an increase in ASAT or ALAT of three times the upper limit of normal or greater persist. LESCOL therapy should be discontinued.** Active liver disease or unexplained transaminase elevations are contraindications to the use of LESCOL (see CONTRAINDICATIONS). Caution should be exercised when LESCOL is administered to patients with a history of liver disease or heavy alcohol ingestion (see PHARMACOLOGY: Pharmacokinetics/ Metabolism). Such patients should be closely monitored. **Skeletal Muscle:** Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has not been reported to date with LESCOL therapy. Myopathy (defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal) has been reported in one LESCOL treated patient to date, which was related to physical exertion. An additional case was reported in a patient receiving placebo. However, because these adverse events have been reported with other drugs of this class, the following cautions are advised. Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK (greater than 10 times the upper limit of normal). Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **LESCOL therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** LESCOL therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma, severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy. An increased risk of myopathy has been reported with another HMG CoA reductase inhibitor (lovastatin) when administered concomitantly with cyclosporine, gemfibrozil, erythromycin, or niacin. There is limited experience to date with the use of LESCOL together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with LESCOL together with niacin. Although the use of fibrates alone or in combination with lovastatin has been occasionally associated with myopathy, in a crossover study to investigate the pharmacokinetic interaction of LESCOL and bezafibrate in 30 volunteers no myopathy was observed.

**PRECAUTIONS – General:** Before instituting therapy with LESCOL (fluvastatin), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of LESCOL or any other lipid-lowering agent. **Homozygous Familial Hypercholesterolemia:** LESCOL (fluvastatin sodium) has not been evaluated in patients with rare homozygous familial hypercholesterolemia. HMG-CoA reductase inhibitors are reported to be less or not effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors. Additionally, studies with other HMG-CoA reductase inhibitors indicate that such treatment appears more likely to raise serum transaminases in these homozygous patients. **Effect on lipoprotein(A) [Lp(a)]:** In some patients the beneficial effect of lowered total cholesterol and LDL cholesterol levels may be partly blunted by a concomitant increase in the Lp(a) levels. Until further experience is obtained from controlled clinical trials, it is suggested, where feasible, that Lp(a) measurements be carried out in patients placed on therapy with LESCOL. **Effect on $CoQ_{10}$ levels (Ubiquinone):** A significant decrease in plasma $CoQ_{10}$ levels in patients treated with LESCOL and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of $CoQ_{10}$ has not yet been established. **Severe Renal Impairment:** Caution is advised in patients with severe renal impairment. **Endocrine Function:** HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. LESCOL exhibited no effect upon non-stimulated cortisol levels, FSH (males only) or thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in an adequate number of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with LESCOL who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones. **Ophthalmic Evaluations:** Current data from clinical trials do not indicate an adverse effect of LESCOL on the human lens. However, long-term effects are not yet established and therefore periodic ophthalmological examinations are recommended taking into consideration that, in the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. **Pregnancy:** LESCOL is contraindicated during pregnancy and in nursing mothers (see CONTRAINDICATIONS). Data on the use of LESCOL in pregnant women is limited. During the clinical program, a total of 5 women who were receiving LESCOL became pregnant and were discontinued from the studies. Of these 5 women, 2 gave birth to healthy babies, one experienced an ectopic pregnancy which was attributed to a severely scarred fallopian tube; and one spontaneously aborted. The outcome for the fifth patient is not yet known. Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. LESCOL should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus (see CONTRAINDICATIONS). **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants, women receiving LESCOL should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Only limited experience with the use of HMG-CoA reductase inhibitors is available in children; however, there is no experience to date with the use of LESCOL in such patients. **Geriatric Use:** The effect of age on the pharmacokinetics of LESCOL was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary either as a function of age or gender. (See also PHARMACOLOGY: Pharmacokinetics/ Metabolism.)

**DRUG INTERACTIONS** – A drug interactive effect (pharmacokinetic and/or clinical) has been shown for the following drugs in combination with LESCOL: *Cholestyramine:* Administration of LESCOL concomitantly 2 to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for the fluvastatin AUC and 50-80% for the fluvastatin $C_{max}$. However, administration of LESCOL 4 hours after cholestyramine resulted in a clinically significant additive effect in reducing total-C and LDL-C compared with that achieved with either component drug (see DOSAGE AND ADMINISTRATION). *Gemfibrozil/Fenofibrate/Niacin:* Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of other HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency. (see WARNINGS: Skeletal Muscle) *Cimetidine/Ranitidine/ Omeprazole:* Concomitant administration of LESCOL with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin $C_{max}$ (43%, 70% and 50%, respectively) and AUC (24 to 33%), with an 18 to 23% decrease in apparent oral plasma clearance (Cl/F). *Digoxin:* In a crossover study involving 18 patients chronically receiving digoxin, concomitant administration of a single 40 mg dose of LESCOL had no effect on digoxin AUC and small but clinically insignificant increases in the digoxin $C_{max}$ and urinary clearance were noted. *Rifampicin:* Administration of LESCOL to subjects pretreated with rifampicin results in significant reduction in $C_{max}$ (59%) and AUC (51%) of fluvastatin, with a large increase (95%) in plasma clearance. In pharmacokinetic studies and in retrospective analysis of the concomitant medications used during clinical studies, LESCOL did not show an interactive effect with the following drugs: *Antipyrine:* Administration of LESCOL does not influence the metabolism and excretion of antipyrine, either by induction or inhibition. Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system; therefore, interactions with other drugs metabolized by this mechanism are not expected. *Niacin/Propranolol:* Concomitant administration of LESCOL with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium. *Warfarin:* In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. However, since other drugs of this class have been shown to enhance the anticoagulant effect of warfarin, caution is advised when administering warfarin concomitantly with LESCOL. *Other Concomitant Therapy:* Although specific interaction studies were not performed, in clinical studies, LESCOL was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, antacids, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant interactions. Although no conclusive studies have been done to date with LESCOL, interactions with the following drugs have been reported with other HMG-CoA reductase inhibitors: *Immunosuppressive Drugs, Erythromycin:* See WARNINGS: Skeletal Muscle. **Laboratory Interactions :** The HMG-CoA reductase inhibitors may cause elevation of creatinine phosphokinase and transaminase levels (see WARNINGS). In the differential diagnosis of chest pain in a patient on LESCOL, cardiac and noncardiac fractions of these enzymes should be determined.

**ADVERSE REACTIONS** – In the controlled clinical studies and their open extensions, 1% of 1881 patients were discontinued due to adverse experiences attributable to LESCOL (fluvastatin sodium) (mean exposure approx. 14 months ranging in duration from one to more than 24 months). When adjusted for duration of exposure this incidence was slightly less for patients receiving

LESCOL compared to those on placebo (0.9% vs. 1.3%). Adverse reactions were usually mild and transient and similar in incidence to placebo. Common adverse experiences possibly attributable to LESCOL at the recommended dose range of 20-40 mg/day which occurred at a > 1% frequency are listed on the chart.

| ADVERSE EVENT | LESCOL (%) (n = 620)+ | Placebo (%) (n = 411) |
|---|---|---|
| **Gastrointestinal** | | |
| Dyspepsia | 6.6% | 3.6% |
| Diarrhea | 3.2% | 3.2% |
| Abdominal Pain | 3.9% | 2.4% |
| Nausea | 2.7% | 1.5% |
| Flatulence | 1.6% | 4.1% |
| Constipation | 1.8% | 3.6% |
| **Musculoskeletal** | | |
| Arthropathy | 1.5% | 1.5% |
| Back pain | 1.3% | 1.7% |
| Myalgia | 1.1% | 1.5% |
| **Central Nervous System** | | |
| Dizziness | 1.8% | 2.2% |
| Abnormal vision | 1.3% | 2.4% |
| **Psychiatric** | | |
| Insomnia | 1.8% | 1.2% |
| **Respiratory** | | |
| Upper respiratory infection | 1.1% | 2.9% |
| **Integumentary** | | |
| Rash | 2.1% | 2.9% |
| **Miscellaneous** | | |
| Headache | 3.5% | 3.6% |
| Fatigue | 2.3% | 2.9% |

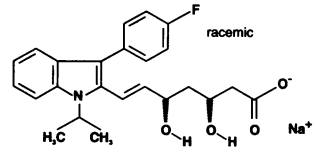
+N = 620 includes all patients who received LESCOL in the core controlled clinical studies

The following effects have been reported with drugs of this class: *Skeletal:* myopathy, rhabdomyolysis (see WARNINGS), muscle cramping/ pain. *Neurological:* paresthesia, peripheral neuropathy, psychiatric disturbances/anxiety. *Hypersensitivity Reactions:* An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors and has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiform, including Stevens-Johnson syndrome. *Gastrointestinal:* hepatitis, cholestatic jaundice, anorexia, vomiting. *Skin:* alopecia. *Miscellaneous:* Asthenia, sweating, hot flashes.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE –** The maximum single oral dose of LESCOL (fluvastatin sodium) received by healthy volunteers was 60 mg. No clinically significant adverse experiences were seen at this dose. There has been a single report of two children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested LESCOL. The maximum amount of LESCOL ingested was 80 mg (4 x 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems. No specific information on the treatment of overdosage can be recommended. Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of LESCOL and its metabolites in man is not known at present.

**DOSAGE AND ADMINISTRATION –** Prior to initiating LESCOL (fluvastatin sodium), the patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the American Heart Association [AHA] Step 1 Diet), which should be continued during treatment. If appropriate, a program of weight control and physical exercise should be implemented. The recommended starting dose is 20 mg once daily at bedtime. The recommended dosing range is 20-40 mg/day as a single dose in the evening. As with other drugs of this class, splitting the larger dose into a BID regimen provides a modest improvement in LDL-C response. LESCOL may be taken without regard to meals, since there are no apparent differences in the lipid lowering effects of LESCOL administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C are seen within 4 weeks of administration of a given dose, periodic lipid determinations should be performed during this time, and periodically thereafter, with dosage adjusted to a maximum of 40 mg/day according to the patient's response to therapy. The therapeutic effect of LESCOL is maintained with prolonged administration. **Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of LESCOL if cholesterol levels fall below the targeted range, such as that recommended by the second report of the U.S. National Cholesterol Education Program (NCEP) Concomitant Therapy:** The lipid lowering effects of LESCOL on total cholesterol and LDL cholesterol are enhanced when combined with a bile-acid binding resin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium concomitantly, LESCOL should be administered at bedtime, at least 4 hours following the resin to obtain a maximal lipid lowering effect. (See PRECAUTIONS, DRUG INTERACTIONS). **Dosage in Patients with Renal Insufficiency:** Since LESCOL is cleared hepatically with less than 5% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not deemed to be necessary. Caution should be exercised with severe renal impairment (see PRECAUTIONS).

**PHARMACEUTICAL INFORMATION – Drug Substance: Proper Name:** fluvastatin sodium – **Chemical Name:** [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy -6-heptenoic acid, monosodium salt – **Empirical Formula:** $C_{24}H_{25}FNO_4 \cdot Na$ – **Molecular Weight:** 433.46. – **Structural Formula:**




**Description:** Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. The pKa value is approximately 5.5. The pH of a 1% solution (w/v) varies between 8.2-10.0 due to trace amounts of residual sodium hydroxide or carbonates. The octanol/water partition coefficient is 6.8. **Composition: Active Ingredient:** fluvastatin sodium. **Inactive Ingredients:** sodium bicarbonate, calcium carbonate, microcrystalline cellulose, pregelatinized starch, talc, magnesium stearate, gelatin, iron oxide red, iron oxide yellow, iron oxide black, titanium dioxide, silicon dioxide, sodium laurel sulphate, benzyl alcohol, sodium propionate, edetate calcium disodium, carboxymethyl cellulose sodium, butyl paraben, propyl paraben, methyl paraben, shellac, polyvinylpyrrolidone, ethyl alcohol, isopropyl alcohol, propylene glycol, n-butyl alcohol, sodium hydroxide, ammonium hydroxide.

**STABILITY AND STORAGE RECOMMENDATIONS –** Store between 15 and 30°C in a tight container. Protect from light and humidity.

**AVAILABILITY OF DOSAGE FORMS – LESCOL Capsules 20 mg:** Each light brown cap and brown body gelatin capsule contains 20 mg fluvastatin (from 21.06 mg fluvastatin sodium). Cap is imprinted with Sandoz triangle and "20"; body is imprinted with "Lescol" and product logo. Available in bottles of 100. **LESCOL Capsules 40 mg:** Each gold cap and brown body gelatin capsule contains 40 mg fluvastatin (from 42.12 mg fluvastatin sodium). Cap is imprinted with Sandoz triangle and "40"; body is imprinted with "Lescol" and product logo. Available in bottles of 100.

PAAB PMAC

*Registered trademark of Sandoz Canada Inc. LES-94-02-2539E
Product Monograph available on request. K33

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*co-promoted by:*

SANDOZ — SANDOZ CANADA INC. Dorval, Quebec H9R 4P5

ASTRA — Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

# Zostrix®

(capsaicin 0.025%)

**Zostrix**. Cream
Capsaicin 0.025%

TOPICAL ANALGESIC

**Description:** Zostrix Cream contains capsaicin, 0.025%, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

**Action:** Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition substance P has been shown to be released into joint tissues and active inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

**Indication:** Zostrix is indicated for the temporary relief of peripheral neuralgias such as the pain following shingles (herpes zoster). Zostrix is also indicated for the temporary relief of the pain associated with arthritis.

**Warnings: FOR EXTERNAL USE ONLY**. Avoid contact with eyes and broken or irritated skin. Do not bandage. Application of external heat may result in excessive skin irritation or burn(s). If condition worsens, or does not improve after 28 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children**. In case of accidental ingestion, seek professional assistance or contact a Poison Control Centre immediately.

**Directions:** Adults and children 2 years of age and older. Apply Zostrix to affected area 3 to 4 times daily. Transient burning may occur upon application, but usually disappears in 72 hours. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands immediately after applying Zostrix.**

**How supplied:** 20g tube
42.5g tube
85g tube

Store at room temperature
DIN 00740306

**References: 1.** Zostrix Drug Monograph, 1992. **2.** Deal CI, Schnitzer TJ, Lipstein E et al: Treatment of arthritis with topical capsaicin: a double-blind trial. Clinical Therapeutics. 1991;13(3): 383-395. **3.** Deal CI, Schnitzer TJ, Lipstein E et al: Treatment of arthritis with topical capsaicin: a double-blind trial. Clinical Therapeutics. 1991;13(3): 383-395. Subset analysis. **4.** Lotz M, Weismen M et al: Effects of topical capsaicin (0.075%) on substance P and prostaglandin E2 in synovial fluid: A double-blind study. Arthritis and Rheumatism 1992; 35(9): Abstract D132, p. S235.

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(acyclovir)

# ZOVIRAX* Tablets, Capsules, and Suspension

**INDICATIONS AND CLINICAL USE:** ZOVIRAX (acyclovir) may be indicated for the following conditions:

The treatment of initial episodes of herpes genitalis.

The suppression of unusually frequent recurrences of herpes genitalis (6 or more episodes per year).

The acute treatment of herpes zoster (shingles) and varicella (chickenpox).

The results of clinical studies suggest that some patients with recurrent genital herpes may derive clinical benefit from the administration of oral ZOVIRAX if taken at the first sign of an impending episode. Those most likely to benefit are patients who experience severe, prolonged recurrences; such intermittent therapy may be more appropriate than suppressive therapy when these recurrences are infrequent.

Early treatment of acute herpes zoster (shingles) in immune competent individuals with oral ZOVIRAX resulted in decreased viral shedding; decreased time to healing; less dissemination; and alleviation of acute pain.

**CONTRAINDICATIONS:** ZOVIRAX (acyclovir) is contraindicated for patients who develop hypersensitivity or who are hypersensitive to the components of the formulations.

Treatment of varicella (chickenpox) in immune competent patients with oral ZOVIRAX reduced the total number of lesions, accelerated the progression of lesions to the crusted and healed stages, and decreased the number of residual hypopigmented lesions. In addition, ZOVIRAX decreased fever and constitutional symptoms associated with chickenpox.

The prophylactic use of acyclovir in chickenpox has not been established.

**WARNINGS:** Suppressive therapy of herpes genitalis with ZOVIRAX (acyclovir) should be considered only for severely affected patients. Periodic evaluation of the need for continued suppressive therapy is recommended. In some patients, there is a tendency for the first recurrent episode to be more severe following cessation of suppressive therapy.

Strains of herpes simplex virus and varicella zoster virus resistant to acyclovir have been reported; there is no clear evidence, however, that there is a clinically significant induction of such strains during intermittent or suppressive therapy for herpes genitalis or acute therapy of herpes zoster in otherwise normal patients. However, in severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses associated with infections which may not respond to continued acyclovir therapy. This, however, remains to be clearly established and should be considered as a factor when undertaking therapy. The effect of the use of ZOVIRAX on the natural history of herpes simplex or varicella zoster infection is unknown.

**PRECAUTIONS: General:** The recommended dosage and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION).

The decision to prescribe a course of suppressive therapy should be weighed in the light of our present knowledge about the long-term effects of ZOVIRAX and must clearly relate to the condition of the patient.

It is suggested that periodic discontinuation of the suppressive regimen occur so that the patient's status and need for continued suppressive therapy can be monitored.

Whereas cutaneous lesions associated with herpes simplex infections are often pathognomonic, Tzanck smears prepared from lesion exudate or scrapings may assist in the diagnosis. Positive cultures for herpes simplex virus offer the only absolute means for confirmation of the diagnosis. Appropriate examinations should be performed to rule out other sexually transmitted diseases.

All patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy.

**Chickenpox:** Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that ZOVIRAX treatment of chickenpox would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life.

**Use in Pregnancy:** Teratology studies carried out to date in animals have been negative. However, since such studies are not always predictive of human response, ZOVIRAX should not be used during pregnancy unless the physician feels the potential benefit justifies the risk of possible harm to the fetus. The potential for high concentrations of acyclovir to cause chromosome breaks *in vitro* should be taken into consideration in making this decision.

**Nursing Mothers:** Acyclovir is excreted in human milk. Caution should therefore be exercised when ZOVIRAX is administered to a nursing mother.

**Use in Children:** Safety and effectiveness in children less than 2 years of age have not been adequately studied.

**Drug Interactions:** Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.

**ADVERSE REACTIONS: Treatment of Herpes Simplex:** The most frequent adverse reactions reported during clinical trials of treatment of genital herpes with oral ZOVIRAX in 298 patients are listed below:

| Adverse Reactions | Total | % | Adverse Reactions | Total | % |
|---|---|---|---|---|---|
| Nausea and/or vomiting | 8 | 2.7 | Headache | 2 | 0.6 |

Less frequent adverse reactions, each of which occurred in 1 of 298 patient treatments (0.3%), included: diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

**Suppression:** The most frequent adverse reactions reported in clinical trials of continuous (up to 12 months) administration of oral ZOVIRAX for the prevention of recurrences in 441 patients were:

| Adverse Reactions | Total | % | Adverse Reactions | Total | % |
|---|---|---|---|---|---|
| Headache | 36 | 8.2 | Arthralgia | 9 | 2.0 |
| Nausea and/or vomiting | 34 | 7.7 | Fatigue | 9 | 2.0 |
| Diarrhea | 30 | 6.8 | Sore throat | 6 | 1.4 |
| Skin rash | 13 | 3.0 | Upset stomach | 5 | 1.1 |
| Vertigo | 12 | 2.7 | | | |

Less frequent adverse reactions, each of which occurred in less than 1% of the 441 patients (see number of patients in parentheses), included: insomnia (4), fever (4), menstrual abnormality (4), acne (3), dysuria (3), lymphadenopathy (2), muscle cramps (2), genital pain (2), back pain (2), irritability (1), accelerated hair loss (1), depression (1), pars planitis (1), palpitations (1), and superficial thrombophlebitis (1).

Evidence so far from clinical trials suggests that the severity and frequency of adverse events is unlikely to necessitate discontinuation of therapy.

**Herpes Zoster:** The most frequent adverse reactions reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral ZOVIRAX 5 times daily for 7 or 10 days or placebo were:

| Adverse Reactions | ZOVIRAX (%) (n=323) | Placebo (%) (n=323) | Adverse Reactions | ZOVIRAX (%) (n=323) | Placebo (%) (n=323) |
|---|---|---|---|---|---|
| Malaise | 11.5 | 11.1 | Vomiting | 2.5 | 2.5 |
| Nausea | 8.0 | 11.5 | Diarrhea | 1.5 | 0.3 |
| Headache | 5.9 | 11.1 | Constipation | 0.9 | 2.4 |

**Chickenpox:** The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral ZOVIRAX or placebo were:

| Adverse Reactions | ZOVIRAX (%) (n=495) | Placebo (%) (n=498) | Adverse Reactions | ZOVIRAX (%) (n=495) | Placebo (%) (n=498) |
|---|---|---|---|---|---|
| Diarrhea | 3.2 | 2.2 | Flatulence | 0.4 | 0.8 |
| Abdominal Pain | 0.6 | 0.2 | Urticaria | 0.2 | 0.2 |
| Rash | 0.6 | 0.2 | Spasmodic Hand Movement | 0.2 | 0.2 |
| Vomiting | 0.6 | 0.2 | Insomnia | 0.2 | 0.4 |

**SYMPTOMS AND TREATMENT OF OVERDOSAGE:** Overdosage of ZOVIRAX (acyclovir) during oral use is unlikely because of incomplete bioavailability from the gastrointestinal tract. Doses as high as 800 mg 6 times daily for 5 days have been administered to humans without acute untoward effects. In clinical studies, the highest plasma concentration observed in a single patient at these doses was 10.0 μg/mL.

Intravenous doses administered to humans have been as high as 1200 mg/m$^2$ (28 mg/kg) 3 times daily for up to 2 weeks. Peak plasma concentrations have reached 80 μg/mL. No acute massive overdosage of ZOVIRAX has been reported; however, in the case of an excessively high ingestion of ZOVIRAX, precipitation of acyclovir in renal tubules may occur if the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. In the event of renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored.

**DOSAGE AND ADMINISTRATION: Herpes Genitalis: Treatment of Initial Infection:** One 200 mg tablet/capsule or one teaspoonful of suspension (5 mL) every 4 hours, while awake, for a total of 1 gram daily for 10 days. Therapy should be initiated as early as possible following onset of signs and symptoms.

**Suppressive Therapy for Recurrent Disease:** The initial recommended dose is one 200 mg tablet/capsule or one teaspoonful of suspension (5 mL) three times daily. This can be increased if breakthrough occurs up to a dosage of one 200 mg tablet/capsule or one teaspoonful (5 mL) of suspension, five times daily. If necessary, a dose of one 400 mg tablet (two 200 mg tablets/capsules) or two teaspoonfuls of suspension (10 mL) given twice daily may be considered. Periodic re-evaluation of the need for therapy is recommended.

Administration of ZOVIRAX for intermittent therapy is one 200 mg tablet/capsule or one teaspoonful (5 mL) of suspension every 4 hours 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

**Herpes Zoster:** One 800 mg tablet, or 800 mg of another oral dosage form, every 4 hours, 5 times daily for 7 to 10 days. Treatment should be initiated within 72 hours of the onset of lesions. In clinical trials, the greatest benefit occurred when treatment was begun within 48 hours of the onset of lesions.

**Treatment of Chickenpox:** 20 mg/kg (not to exceed 800 mg) orally, 4 times daily for 5 days. Therapy should be initiated within 24 hours of the appearance of rash.

**Patients With Acute or Chronic Renal Impairment:** Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment.

Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

| Normal Dosage Regimen (5× daily) | Creatinine Clearance (mL/min/1.73m$^2$) | Adjusted Dosage Regimen | |
|---|---|---|---|
| | | Dose (mg) | Dosing Interval (hours) |
| 200 mg every 4 hours | >10 | 200 | every 4 hours, 5× daily |
| | 0-10 | 200 | every 12 hours |
| 400 mg every 12 hours | >10 | 400 | every 12 hours |
| | 0-10 | 200 | every 12 hours |
| 800 mg every 4 hours | >25 | 800 | every 4 hours, 5× daily |
| | 10-25 | 800 | every 8 hours |
| | 0-10 | 800 | every 12 hours |

For patients who require hemodialysis, the dosing schedule should be adjusted so that a dose is administered after each dialysis.

**DOSAGE FORMS: ZOVIRAX 200 Tablets:** Each blue, shield-shaped, bevel-edged, compressed tablet imprinted with "ZOVIRAX" on one side and a triangle on the reverse contains 200 mg acyclovir and the non-medicinal ingredients lactose, cellulose, sodium starch glycolate, povidone, magnesium stearate and indigotine. Available in bottles of 100 and 250 tablets. **ZOVIRAX 400 Tablets:** Each pink, shield-shaped, bevel-edged, compressed tablet imprinted with "ZOVIRAX 400" on one side and a triangle on the reverse contains 400 mg acyclovir and the non-medicinal ingredients cellulose, sodium starch glycolate, povidone, magnesium stearate and iron oxide. Available in cartons of 4 blister-packs of 14 tablets each (56 tablets). **ZOVIRAX 800 Tablets:** Each blue, biconvex, elongated, scored, compressed tablet imprinted with "ZOVIRAX 800" on one side contains 800 mg acyclovir and the non-medicinal ingredients cellulose, sodium starch glycolate, povidone, magnesium stearate and indigotine. Available in cartons of 50 blister-packed tablets. **ZOVIRAX Capsules:** Each opaque, blue capsule imprinted "Wellcome ZOVIRAX 200" contains 200 mg acyclovir and the non-medicinal ingredients lactose, corn starch, magnesium stearate and sodium lauryl sulfate; hard gelatin capsule contains indigotine and other ingredients; printed with edible black ink. Available in bottles of 100 capsules. **ZOVIRAX Suspension:** Each teaspoonful (5 mL) of off-white suspension contains 200 mg of acyclovir and the non-medicinal ingredients sorbitol, glycerin, cellulose, methylparaben, propylparaben, vanillin and banana flavour. Available in bottles of 125 mL.

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**References: 1.** Limandri BJ: Disclosure of stigmatizing conditions: The discloser's perspective. *Arch Psychiatr Nurs* 1989;3(2):69-78. **2.** Keller ML, Jadack RA, Mims LF: Perceived stressors and coping responses in persons with recurrent genital herpes. *Res Nurs Health* 1991;14:421-430. **3.** Christensen C, Kitsikis T: Psychosocial dimensions of genital herpes: A case study approach. *Journal of Social Work and Human Sexuality* 1988;6(2):89-104. **4.** Kaplowitz LG, Baker D, Gelb L, et al: Prolonged continuous acyclovir treatment of normal adults with frequently recurring genital herpes simplex virus infection. *JAMA* 1991;265(6):747-751.



Product Monograph available on request.

# Mobiflex®
**(Tenoxicam) Tablets 20 mg**

**PHARMACOLOGICAL CLASSIFICATION**
**Anti-inflammatory, Analgesic Agent**


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Product Monograph available to health professionals upon request.
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**ACTIONS AND CLINICAL PHARMACOLOGY**

'Mobiflex' (tenoxicam) is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties. Its mechanism of action, as with other non-steroidal anti-inflammatory agents, is not yet completely known. Tenoxicam is an inhibitor of prostaglandin biosynthesis both in vitro and in vivo (protects mice against arachidonic acid induced toxicity). In vitro tests of leucocyte peroxidase also suggest that tenoxicam may act as a scavenger for active oxygen at the site of inflammation. These effects probably explain in part, the activity of 'Mobiflex' in the treatment of painful inflammatory and degenerative diseases of the musculoskeletal system. 'Mobiflex' does not act by pituitary-adrenal stimulation.

After 4, 7, 10 or 14 days of culture with tenoxicam (2.4, 12, 48 µg/mL), there was no significant effect on the amount of cartilage proteoglycans synthesized and released into the culture medium of human chondrocytes, as compared to untreated cultures.

In vitro studies have also shown that tenoxican inhibits the activity of both proteoglycanase and collagenase enzymes obtained from human osteoarthritic cartilage. These in vitro results suggest a positive effect of tenoxicam on the joint cartilage under experimental conditions by slowing down the enhanced catabolism of the osteoarthritic cartilage matrix. The clinical significance of these findings is not yet known and is being investigated.

**INDICATIONS**

'Mobiflex' (tenoxicam) is indicated for the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and extra-articular inflammations such as tendinitis, bursitis, and periarthritis of the shoulders or hips.

**CONTRAINDICATIONS**

'Mobiflex' (tenoxicam) should not be administered to patients with active peptic ulcer or active inflammatory diseases of the gastrointestinal tract. 'Mobiflex' is contraindicated in patients who have shown hypersensitivity to the drug. It should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

Before anesthesia or surgery, 'Mobiflex' should not be given to elderly patients, to patients at risk of renal failure, or to patients with increased risk of bleeding, because of an increased risk of acute renal failure and possibility of impaired hemostasis.

**WARNINGS**

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAID's) including 'Mobiflex' (tenoxicam).

Caution should be exercised when a NSAID such as 'Mobiflex' is used in patients with a history suggestive of peptic ulcer, melena, or any gastrointestinal disease. In these cases, the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). As with other non-steroidal anti-inflammatory drugs, 'Mobiflex' should be used with special caution in these patients.

**Use in Pregnancy and Lactation** The safety of 'Mobiflex' (tenoxicam) during pregnancy and lactation has not been established and therefore its use during pregnancy and lactation is not recommended.

No teratogenic effects were observed in animal reproductive studies. Rats receiving tenoxicam during pregnancy showed delayed delivery. Tenoxicam readily passes into the milk of lactating rats.

**Use in Children** 'Mobiflex' (tenoxicam) is not recommended for use in patients under 16 years of age as the dose and indications in this population have not been established.

**PRECAUTIONS**

**Gastro-intestinal System** If peptic ulceration or gastrointestinal bleeding occur in patients under treatment with 'Mobiflex' (tenoxicam), the drug should be immediately withdrawn.

There is no definitive evidence that the concomitant administration of histamine $H_2$-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of 'Mobiflex' therapy when and if these adverse reactions appear.

**Renal function** As with other nonsteroidal anti-inflammatory drugs, long-term administration of tenoxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Reversible elevation of BUN and serum creatinine have been reported with 'Mobiflex'. The effect is thought to result from inhibition of renal prostaglandin synthesis resulting in changes in medullary and deep cortical blood flow with an attendant effect on renal function. Patients with impaired renal function or on diuretics, as well as elderly patients and those with congestive heart failure or liver ascites, are more at risk.

During long-term therapy, kidney function should be monitored periodically.

**Hepatic Function** As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically.

**Fluid and Electrolyte Balance** Fluid retention and edema have been observed in patients treated with 'Mobiflex'. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart-failure in elderly patients or those with compromised cardiac function should be born in mind. 'Mobiflex' should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With NSAID treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; and patients receiving concomitant therapy with B-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

**Hematology** Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when 'Mobiflex' is administered.

Blood dyscrasias associated with the use of non-steroidal anti-inflammatory drugs is rare, but could be with severe consequences.

**Infection** In common with other anti-inflammatory drugs 'Mobiflex' may mask the usual signs of infection.

**Ophthalmology** Blurred and/or diminished vision has been reported with the use of 'Mobiflex' and other non-steroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

**Hypersensitivity Reactions** As with other NSAID's, allergic reactions may occur. Manifestation of allergic reactions include urticaria, bronchospasm and anaphylaxis, and in rare instances, severe skin reactions such as Stevens-Johnson syndrome and Lyell Syndrome.

**Drug Interactions Acetylsalicylic Acid or Other NSAID's** Plasma concentrations of tenoxicam are reduced to approximately 80% of their normal concentrations when single doses of 'Mobiflex' (tenoxicam) are administered in conjunction with acetylsalicylic acid (2,600 to 3,900 mg/day). At steady state, simultaneous administration of ASA does not appear to have a significant effect on the plasma concentration of tenoxicam. The use of 'Mobiflex' in conjunction with acetylsalicylic acid or another nonsteroidal anti-inflammatory agent is not recommended since data are not available demonstrating that the combination produces greater improvement than that achieved with either drug alone, and the potential for adverse reactions is increased.

**Protein-Bound Drugs** As with other NSAID's, 'Mobiflex' is highly protein-bound, and therefore, might be expected to displace other protein-bound drugs, such as anticoagulants, oral hypoglycemics (sulfonylureas), phenytoin, and sulfonamides.

Short term pharmacodynamic studies have demonstrated that tenoxicam does not potentiate the anticoagulant effect of coumarin-type anticoagulants nor the hypoglycemic effect of sulfonylurea drugs. However, when a NSAID such as 'Mobiflex' is administered concomitantly with anticoagulants, oral hypoglycemics, or other highly protein bound drugs, the patients should be monitored and dosage adjustments made, if necessary.

**Diuretics/Antihypertensives** As with other nonsteroidal anti-inflammatory drugs, 'Mobiflex' can attenuate the blood pressure lowering effect of hydrochlorothiazide and the peak excretion rates of Na+ and C1- in patients with hypertension. Therefore, close monitoring of patients on this drug combination is advisable. The excretion of electrolytes was not significantly affected when tenoxicam (two-day loading dose of 40 mg daily, followed by 20 mg daily) was administered to normotensive patients receiving furosemide therapy (40 mg daily).

Some NSAID's have been reported to reduce the antihypertensive effects of certain beta-blockers. The interaction between 'Mobiflex' and beta-blockers has not been studied.

**Digoxin** In elderly patients, with normal plasma creatinine levels, plasma digoxin levels were not altered by the concomitant administration of 'Mobiflex' (30 mg daily).

**Antacids** The administration of 15 mL of an aluminum hydroxide or an aluminum and magnesium hydroxide antacid just prior to a single 20 mg oral dose of 'Mobiflex' did not affect the bioavailability of tenoxicam.

**Cholestyramine** The average half-life of tenoxicam, after a single 20 mg intravenous dose, was reduced from 67.4 hours to 31.9 hours following the administration of cholestyramine (4 g in 200 mL water p.o. t.i.d.). The apparent drug clearance of tenoxicam increased by 105%.

**Lithium** Nonsteroidal anti-inflammatory agents have been reported to increase steady state plasma lithium concentrations. It is recommended that these concentrations be monitored when initiating, adjusting and discontinuing 'Mobiflex' treatment.

**Methotrexate** The co-administration of some NSAID's and methotrexate has been associated with reduced renal tubular secretion of methotrexate, higher plasma concentrations, and severe methotrexate toxicity. Therefore, caution should be exercised when NSAID's, such as 'Mobiflex', are administered concurrently with methotrexate. The interaction between 'Mobiflex' and methotrexate has not been studied.

**ADVERSE REACTIONS**

The most common adverse reactions encountered with non-steroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

In approximately 12,000 patients administered 'Mobiflex' (tenoxicam) 10-40 mg/day, (approximately four/fifths receiving 20 mg/day), the incidence of peptic ulceration and the incidence of gastrointestinal bleeding (including hematemesis and melena) was 0.1-0.6%.

Approximate incidences of other adverse effects over 1% listed by systems are reported below. For a complete list of adverse effects, refer to the PRODUCT MONOGRAPH.

**Gastrointestinal:** (10.4-23.0%)
Dyspepsia (0.1-9.7%), nausea (2.0-6.7%), constipation (0.5-2.9%), abdominal pain (0.7-3.3%), diarrhea (0.5-2.3%), flatulence (0.04-1.9%), vomiting (0.2-1.1%), abdominal discomfort (1.4-2.2%), pyrosis (1.3-1.9%), epigastric pain (1.8-2.5%), gastric pressure (0.5-1.0%).
**Dermatologic:** (1.6-3.9%) Rash (0.2-1.4%), pruritis (0.3-1.3%).
**Central Nervous System:** (2.0-9.1%) Headache (0.9-4.3%), dizziness (0.8-3.3%).
**Renal:** Edema (0.2-1.3%).

**DOSAGE AND ADMINISTRATION**

A single daily dose of 20 mg 'Mobiflex' (tenoxicam) should be taken orally at the same time each day. Higher doses should be avoided as they do not usually achieve a significantly greater therapeutic effect, but may be associated with a higher risk of adverse events.

In some patients a 10 mg (1/2 tablet) daily dose may be sufficient. The smallest effective dose should be prescribed.

**Use in Elderly** As with other NSAID's, 'Mobiflex' should be used with special caution in elderly patients since they may be less able to tolerate side effects than younger patients. They are also more likely to be receiving concomitant medication or to have impaired hepatic, renal or cardiovascular function.

**AVAILABILITY**

'Mobiflex' (tenoxicam) tablets 20 mg are available in white, opaque high density polyethylene bottles containing 100 tablets.

The tablets are yellow, film-coated, oblong, single scored on one side, imprinted 'ROCHE'.

**REFERENCES**


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| 15 juin | 13 mai |

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C- 6 Matériel à usage médical
C- 7 Divers
C- 8 Bureaux et locaux à louer
C- 9 Agences de placement
C-10 Postes vacants
C-11 Demandes de postes
C-12 Cabinets à vendre
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**VISA, MASTERCARD ET AMERICAN EXPRESS ACCEPTÉS**

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*En annonçant dans le JAMC, vous êtes assurés d'être publié à près de 60 000 exemplaires deux fois par mois.*

## CONFERENCES

**CANADIAN ASSOCIATION OF EMERGENCY PHYSICIANS, 1994 ANNUAL GENERAL MEETING AND SCIENTIFIC ASSEMBLY: BC** – "Controversies in Emergency Medicine", June 6-9, 1994, Kelowna, BC, Canada. For further information: CAEP Conference, 303-1664 Richter St., Kelowna, BC V1Y 8N3; tel/fax (604) 763-5556. -7176

**IMMUNIZATION IN THE 90s: CHALLENGES AND SOLUTIONS: PQ** – Oct. 5 - 7, 1994, The Quebec Hilton, Quebec City, Quebec. Objectives: to present a forum for the discussion and exchange of ideas related to the practical aspects of immunization programs in Canada. The conference will cover issues such as vaccine supply and delivery, multiplication of vaccines and heavier schedules, education, assessment of vaccine programs (vaccine coverage, immunization records, cold chain, surveillance of adverse events), obstacles to immunization, regulations and legislations, and global immunization efforts. Primary focus will be on childhood immunization. Organized by the Laboratory Centre for Disease Control, Health Canada, with support from the private sector. Call for abstracts: time has been allotted within the conference for peer-reviewed presentations (poster and oral) that relate to the objectives of the conference. Health units are also encouraged to submit proposals for presentations of material related to education and promotion. Abstract submission forms, which can be acquired from the office listed below, must be received before June 3, 1994. To receive a registration package/abstract submission form, contact: Mr. Chuck Schouwerwou, Conference and Committee Coordinator, Childhood Immunization Division, Bureau of Communicable Disease Epidemiology, Laboratory Centre for Disease Control, 2nd flr, LCDC Bldg., Tunney's Pasture, Ottawa, ON K1A 0L2; tel (613) 957-1352, fax (613) 998-6413. -7269

## CONTINUING EDUCATION

**4TH ANNUAL CANADIAN THERAPEUTICS UPDATE: ON** – Sponsored by the Canadian Society for Clinical Pharmacology, July 15-17, 1994, Queen's Landing Inn, Niagara-on-the-Lake, Ontario. Featuring the Shaw Festival and the Niagara wine country. Registration $200; CME credits pending. Contact the Course Director, Dr. David Spence, Department of Medicine, Victoria Hospital, 370 South St., London, ON, Canada N6A 4G5; tel (519) 667-6714, fax (519) 667-6731. -7063

## FELLOWSHIPS

**SUBSPECIALTY TRAINEE/FELLOWSHIP POSITIONS: BC** – The Department of Pediatrics at the University of British Columbia invites applications for fellows/subspecialty trainees in divisions as listed below. These are 1-year appointments renewable for up to 3 years. Training occurs at B.C.'s Children's Hospital, the only university-affiliated tertiary care centre for children in British Columbia. At least 3 core years of pediatric training is required by the following divisions: biochemical diseases (including cystic fibrosis and inborn metabolic disease), cardiology, developmental pediatrics, endocrinology, gastroenterology, hematology/oncology, infectious and immunological diseases, neonatal-perinatal medicine, nephrology, and rheumatology. The Pediatric Intensive Care Unit will accept 3 years of core training in pediatrics or anesthesia, and the Division of Neurology requires a minimum of 1 core year of pediatrics. In accordance with Canadian immigration requirements, this advertisement is directed at Canadian citizens and permanent residents. The University of British Columbia encourages all qualified applicants, especially women, aboriginal people, visible minorities, and persons with disabilities. Salary is commensurate with qualifications and experience. Reply to: Head of the appropriate division, c/o B.C.'s Children's Hospital, 4480 Oak St., Vancouver, BC V6H 3V4. -7309

**TEACHING FELLOWSHIP: BC** – The Department of Pediatrics, University of British Columbia, at British Columbia's Children's Hospital, is inviting applications for a teaching fellow commencing July 1, 1994. Duties involve teaching in the undergraduate programs and other educational responsibilities in the Department of Pediatrics. This is a 1-year appointment based on a 40-hour work week with no call-duties. Three years of core pediatric training is required. Salary will be commensurate with qualifications and experience. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. UBC welcomes all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. Please send curriculum vitae to: Dr. Joan Fraser, U.B.C. Department of Pediatrics, British Columbia's Children's Hospital, Rm. 2D12, 4480 Oak St., Vancouver, BC V6H 3V4. -7235

## LOCUM TENENS AVAILABLE

**GENERAL SURGEON:** – FRCSC, FACS, available for short-term (1 - 4 weeks) locum tenens position. Will travel anywhere in Canada. Reply to: Box 560, CMAJ. -7288

## LOCUM TENENS WANTED

**EMERGENCY MEDICINE: BC** – Locum for 6 months beginning March 1995. Busy urban community hospital. Fellowship or extensive experience in high volume setting mandatory. Reply to: Box 555, CMAJ. -7276

**GASTROENTEROLOGIST: BC** – Aug. 22 - Oct, 31, 1994 in Victoria, British Columbia. Experience in therapeutic ERCP preferred. Could lead to permanent position as eighth member of the existing G.I. group. Reply to: Mr. K. Neumann, tel (604) 595-4305 or fax (604) 595-1738. -7329

**URGENT CARE CENTRE: ON** – Two locum tenens required for July and August by well-established group of 16 emergency physicians who staff two urgent care clinics in Kitchener-Waterloo. Practice similar to that of an emergency department without the emergent case-mix. Experience in emergency procedures, i.e. suturing, fracture care and slit lamp required, as well as ACLS, CMPA. Generous remuneration, no night shifts. Reply with CV to: Dr. Keith Burk, Medical Director, K-W Urgent Care Clinic, 385 Fairway Rd., Kitchener, ON N2C 2N9; tel (519) 748-2327. -7299

**SUMMER LOCUMS - EMERGENCY DEPARTMENT: ON** – Emerge Niagara is an emergency physicians group providing clinical and educational support to Hotel Dieu Hospital. We work with local family physicians to staff the emergency department. Annual patient census is 32 000 - 34 000 visits. Fee-for-service remuneration. Minimum guarantees. ACLS and ATLS required. Future full-time opportunities may be available. St. Catharines is a city of 130 000 in the Niagara fruit belt. Many diverse cultural and recreational activities are available. Proximity to Toronto and Buffalo, approximately 60 minutes. Please send application to: Emerge Niagara, PO Box 107, 109 Martindale Rd., St. Catharines, ON L2S 2Y7; fax (905) 684-6760. -7284

**FAMILY PRACTICE: BC** – Ladysmith, Vancouver Island. Locum needed for summer relief for July and August. One-in-nine on call. No obstetrics. Group of six physicians. Twenty minutes to Nanaimo and Duncan. Call Peter at (604) 245-2235 or fax (604) 245-3094. -7287

**FAMILY PRACTICE: BC** – Locum required for a busy practice in Hope, British Columbia. This is a country practice 157 km from Vancouver, new and well equipped. Obstetrics and gynecology an asset. Hope is a friendly town with skiing, fishing, hockey and an exceptional nine-hole golf course. We have a hospital and a long-term care unit. Please call Dr. David Singleton at (604) 869-7118. -7272

**FAMILY PRACTICE POSITION: BC** – For June and August. Lovely scenic coastal town in northern BC, great salmon fishing. Busy three-physician clinic. Call one in seven and 1 weekend in 4, more if desired. Excellent remuneration. Write: City Centre Medical Clinic, 284 City Centre, Kitimat, BC V8C 1T6; or tel (604) 632-6131, or fax (604) 632-2092. -7260

**FAMILY PRACTICE: BC** – Long-term locum with view to permanent position in a two-physician clinic health care centre, with lab and x-ray facilities. Located in a small mining town in BC Rockies, with excellent recreational facilities and friendly working environment. Average income approximately $100,000 per annum. Call one in two. Please reply to: Box 537, CMAJ. -9893

**FAMILY PRACTICE: BC** – Long-term, full-time locum tenens required (with view to associateship or purchase, if mutually compatible) in a busy office with six general practitioners. Excellent call schedule, one in twelve, 60/40 on gross billing of $150 000 - $200 000/annum. Fine colleagues and good year-round recreational facilities make this city an outstanding place to live and work. Swimming, hiking, skiing, sailing enthusiasts, triatheletes, and couch potatoes welcome. Come join us. Contact: Ms. Janet Knopp, Fraserview Medical Associates, 32-665 Front St., Quesnel, BC V2J 2K9; tel (604) 992-3899, fax (604) 992-7587. -9890

**LOCUM TENENS: NB** – Required for maternity leave from April to June 1994. Busy office practice in Moncton, NB. Tel Dr. M. Conrod, (506) 853-5128 (bus.), (506) 858-7106 (res.). -7068

**FIVE-PHYSICIAN PRACTICE: ON** – Requires a locum tenens for busy rural/urban practice, 20 minutes from Ottawa, July 1, 1994 - Aug. 15, 1994. Our practice is exciting, varied and close enough to Ottawa to have good specialist support. Please reply to: Dr. Lisa Rosenkrantz, 119 Langstaff Dr., PO Box 218, Carp, ON K0A 1L0; or tel (613) 839-3271. -7283

**PHYSICIAN: ON** – Locum wanted from June 24 to Aug. 22, 1994 for extremely busy southwestern Ontario practice run by husband and wife team. Excellent earning potential. Please reply in confidence to: Dr. Roland S. Arnold, Highland Road Medical Centre, 403 - 409 Highland Rd. W, Kitchener, ON N2M 3C6; tel (519) 579-4150, fax (519) 579-2665. -7279

## LOCUM TENENS WANTED

**FAMILY PHYSICIAN/GENERAL PRACTITIONER: ON** – For July and August 1994, or long term. Busy, three-doctor cottage country practice in Northbrook, Ontario, a growing area. No hospital work or obstetrics necessary. No call. Expenses 29%. New modern clinic. Tel Dr. Tobia, (613) 336-8888 (days), (613) 336-9430 (after hours). –7164

**GROUP PRACTICE: ON** – Locum required for July to mid-September 1994 in Chesley, Ontario. ATLS and ACLS preferred; obstetrics optional. Excellent income in a congenial group practice, 30 minutes from Lake Huron's beaches and Bruce Peninsula. For information, tel (519) 363-3220 (weekdays), (519) 363-3595 (evgs.); or write: PO Box 389, Chesley, ON N0G 1L0. –7110

**FAMILY PRACTICE POSITIONS: PE** – The Medical Society of Prince Edward Island is currently seeking locums for the 1994 summer and fall months for family practices in various areas of the province. Compensation for physician services is on a fee-for-service basis. For further information, please contact: Gail Millar, The Medical Society of Prince Edward Island, 559 North River Rd., Charlottetown, PE; tel (902) 368-1572. –7271

**RADIOLOGIST: AB** – Required full time for July and August 1994 in private office practice in Calgary, Alta. (with view to associateship or partnership if mutually agreeable). Excellent remuneration. General radiography, ultrasound and mammography. FRCPC required and eligibility for licensure in Alberta. Reply in confidence to: Dr. G. Yemen, Marlborough Professional Bldg., 210-433 Marlborough Way NE, Calgary, AB T2A 5H5; fax (403) 569-8097, tel (403) 273-9002. –7173

**RADIOLOGY LOCUM: PE** – A radiologist is required for a 3-week period in September/October 1994. Please contact: Dr. John Soutar, Prince County Hospital, Summerside, PE C1N 2A9; tel (902) 436-9131. –7216

**ORTHOPEDIC SURGEON LOCUM: ON** – July 1 - Sept. 1, 1994, Brantford, Ontario. Busy practice. Share call with three other orthopedic surgeons. For further information call: Dr. Chris Whately, (519) 753-8641, ext. 246. –7306

## MISCELLANEOUS

**COMPUTAX ACCOUNTING CENTRE: ON** – Over 25 years of experience in accounting and bookkeeping, specializing in the medical profession. Preparation of A/R of non-OHIP billings, reconciliation of OHIP and WCB billings, monthly financial statements, payroll and personal income tax. 504-2828 Bathurst St., Toronto, ON M6B 3A7; tel (416) 785-9160. –7160

**THE WOLFRAM SYNDROME REGISTRY, NEW YORK MEDICAL COLLEGE: NEW YORK, US** – Conditions: The Wolfram Syndrome Registry in Hawthorne, New York seeks additional Wolfram syndrome (DIDMOAD) patients and their families for federally funded genetic studies. The Wolfram syndrome is diagnosed when diabetes mellitus and bilateral optic atrophy are present. Many other clinical manifestations may occur. Contact: Dr. Ronnie Gorman Swift, Director, Division of Psychiatric Genetics, New York Medical College, 4 Skyline Dr., Hawthorne, NY 10532; tel (914) 347-2690. –7296



## OFFICE SPACE FOR RENT

**SPECIALISTS NEEDED: ON** – In order to enhance the services offered at The Quarry Medical Centre in the Upper Beaches-Fallingbrook area of Scarborough, Ontario, we are looking for orthopedic surgeons, sports medicine specialists, and physical medicine/rehabilitation specialists to join this first class facility. There are currently seven family physicians, a diagnostic radiology and ultrasound clinic, a dental surgeon, and a pharmacy in the building. The Quarry Medical Centre is part of The Quarry Village Plaza, a friendly and very well-maintained neighbourhood landmark which is wheelchair accessible and has ample parking. Scarborough General Hospital, Scarborough Grace Hospital, and Toronto East General and Orthopaedic Hospital are all nearby. Please contact Jack Mandos, tel (416) 693-4611 for more information and to arrange to view the premises. –7305

**OFFICE SPACE FOR RENT: ON** – Doctor required immediately to sublet large office during mornings only in Smyth Medical Center in Ottawa. A prestigious three-story building which has family physicians, dentists and a wide range of specialists; also a laboratory, x-ray and pharmacy. Wheelchair access, 3 elevators, ample underground parking and located 5 minutes from three community hospitals. Please call Martha, between 1 and 5 pm, at (613) 526-0254. –7241

**PROFESSIONAL BUILDING, RICHMOND: ON** – Space suited for medical clinic in professional building. Adjacent to dental practice and pharmacy. Excellent parking. Call Roger Beckley or Kaiser Ahmed, (613) 728-2664, Coldwell Banker First Ottawa Realty. –7238

**CLINIC SPACE AVAILABLE FOR TWO: ON** – Join three busy family physicians in east Ottawa suburb of Orleans. Shared expenses, computerized, fully equipped. Available for June 1994. Please contact: Dr. Sharon Grainger or Dr. Paul McCarthy, tel (613) 837-5454. –7123

**MEDICAL OFFICE SPACE, ST. CATHARINES: ON** – Available immediately, north-end location. Well-maintained, established medical centre including family physicians, cardiologist, laboratory, x-ray/ultrasound, pharmacy, physiotherapy, dentists, optometrist. Wheelchair access, elevator, ample parking. Community hospitals less than 10 minutes away. Attractive leasing options available. Please call Alice Sirard (416) 935-1100. –9859

## PLACEMENT AGENCIES

**LOOKING FOR A LOCUM IN ONTARIO? OR A PRACTICE? PARTNERSHIP?** – Contact: Ontario Medical Association Placement Service, June Dyson, 525 University Ave., Ste. 300, Toronto, ON M5G 2K7; tel (416) 340-2908 or (800) 268-7215 (Ontario). Current listings updated weekly to help you find the position you have in mind. –7014



**US PLACEMENT BY PHYSICIAN:** – Canadian born and educated physician now practising in the US wishes to share his good fortune with others. Residency training preferred. Family practice, obstetrics/gynecology, pediatrics and internal medicine. Immediate openings. I did it and can help you to relocate. Very rewarding. Mail CV to: MD Placement, 5627 North Meridian St., Indianapolis, IN 46208; or fax (317) 353-0287. –7186

## PLACEMENT AGENCIES

**GENERAL PRACTITIONERS/SPECIALISTS:** - Texas: general practitioner, $100 000-120 000 US yearly. Russia: general practitioner for around 3 months. New Zealand: short/long-term anesthetist pediatrician, orthopedist, radiologist. Contact: Pace, tel (604) 266-6020, fax (604) 266-6089. -7314

## POSITIONS VACANT

**The Salvation Army**
**Captain William Jackman**
**Memorial Hospital**
**ANESTHETIST**

Good surgical facilities are provided in a 35-bed fully accredited general hospital serving approximately 15 000. The anesthetist is a sole practice position. The candidate must be eligible for registration with the Newfoundland Medical Board.
The community has excellent sports, recreational and educational facilities.
Please contact as soon as possible.

**Captain Dennis Brown, Executive Director**
**The Salvation Army Captain William Jackman Memorial Hospital**
**410 Booth Ave.**
**Labrador City, NF A2V 2K1**
**Tel (709) 944-2632 (collect)**
**Fax (709) 944-9341** -7295

**ANESTHETIST: ON** - The Sarnia General Hospital and St. Joseph's Health Centre, progressive community hospitals, are seeking an anesthetist with a Canadian fellowship in anesthesia to join their departments of anesthesia. The hospitals perform a total of 12 500 operations per year (9200 general anesthesia); and anesthetists are actively involved in the ICU. The hospitals have excellent support services including radiology, CT, laboratory and pathology. The position is fee for service and the candidate must have or be able to obtain an OHIP billing number. The candidate would share work and call with five other anesthetists. All specialties except cardiac and neurosurgery are represented. Contact: Robert Beauchamp, MD, or Brendan O'Leary, MD, c/o Human Resources, Sarnia General Hospital, 220 N Mitton St., Sarnia, ON N7T 6H6; or phone (519) 383-8174, ext. 5245. Closing date: May 15, 1994. -7294

**ANESTHETIST: ON** - Humber Memorial Hospital, a 263-bed community hospital in northwest metro Toronto requires an anesthetist to provide anesthetic services for busy departments of surgery and outpatients. Must possess FRCPC or be fellowship eligible. Proficiency in general anesthesia services including invasive monitoring, ICU procedures and all aspects of resuscitation is required. Position available July 1, 1994. Deadline for application, May 31, 1994. Please reply in confidence to: Dr. Derek Davidson, Chief of Staff, Administration Office, Humber Memorial Hospital, 200 Church St., Weston, ON M9N 1N8. -7245

**HEAD, DIVISION OF CARDIOLOGY: BC** - The UBC Department of Medicine is seeking applicants for the Heart and Stroke Foundation Chair in Cardiology as the full-time academic (tenure-track) Head of the Division of Cardiology. An FRCPC or equivalent in cardiology is a prerequisite for this senior position. Candidates must have a distinguished record in research, teaching, administration and coordination of delivery of care. The individual will be responsible for the development and coordination of the entire division which is made up of programs located at all of UBC's teaching hospitals. Salary will be commensurate with qualifications and experience. Start date is July 1, 1994. Please submit a letter of application, a CV, a statement of areas of expertise and strengths and the names of three referees, no later than May 30, 1994, to: Dr. G.B. John Mancini, Head, UBC Department of Medicine, University Hospital - UBC Site, 2211 Wesbrook Mall, Vancouver, BC V6T 1Z3. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. UBC encourages all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. -7308

**HEAD, DIVISION OF CARDIOLOGY: BC** - The Department of Pediatrics, University of British Columbia, and B.C.'s Children's Hospital, seek a qualified candidate for head of the division of cardiology. This division serves the province of British Columbia for all tertiary care related to cardiac disorders in infants and children. This is a full-time grant tenure track appointment at the assistant professor rank. Applicants should have a strong background in clinical or basic research, excellent teaching and clinical skills and appropriate administrative experience with proven leadership abilities. Anticipated start date is Sept. 1, 1994; salary will be commensurate with qualifications and experience. The University of British Columbia welcomes all qualified applicants, especially women, aboriginal people, visible minorities, and persons with disabilities. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Please send curriculum vitae by July 31, 1994, to: Dr. Judith G. Hall, Professor and Head, Department of Pediatrics, B.C.'s Children's Hospital, 4480 Oak St., Vancouver, BC V6H 3V4. -7304

**CARDIOLOGIST: ON** - Peel Memorial Hospital has an immediate requirement for a dual-certified internist to join the present group of four cardiologists. The successful candidate will have strong clinical skills including echocardiography, intensive care and pacemaker followup. Peel Memorial Hospital is a busy 422-bed community hospital situated in Brampton, approximately 35 minutes from Toronto. Please send enquiries and curriculum vitae to: Dr. David Borts, Chief, Department of Internal Medicine, Peel Memorial Hospital, 20 Lynch St., Brampton, ON L6W 2Z8. -7311

**DERMATOLOGIST: ON** - Needed for busy practice in southern Ontario border city. Opportunity to work part time in US. Reply to: Box 535, CMAJ. -7009

**GP/SURGEON: AB** - Busy rural practice wishes to acquire a GP/surgeon. Pincher Creek is located in southwest Alberta in the foothills of the Canadian Rockies and close to Waterton Lakes National Park. Excellent indoor and outdoor activities. New hospital, serving area of 10 000, 30 acute and 22 long-term beds. Private clinic associated with department of family practice in Calgary (resident and student teaching); 4 months paid holiday on achievement of parity. Contact: Fay Irving, PO Box 549, Pincher Creek, AB T0K 1W0; tel (403) 627-3321 or fax (403) 627-2280. -7159

**FAMILY PHYSICIAN: AB** - Practice in Edson, Alberta requires family physician to replace leaving female colleague. Group of eight physicians in busy practice; 41-bed hospital and 50-bed nursing home. Obstetrics would be an asset, but we would be interested in a range of skills which would benefit any rural practice. ATLS/ACLS would also be beneficial. We have several visiting specialists. Edson is situated halfway between Edmonton and Jasper. Population 8000, practice 12 000. Excellent summer and winter sports, indoor swimming pool. We offer early partnership or associate arrangement with percentage of gross. Send CV or contact: Dr. Brian Willis, PO Box 6660, Edson, AB T7E 1V1; tel (403) 723-3366 or (403) 723-4502 (evgs.). -7157

**GENERAL PRACTITIONER/ANESTHETIST: AB** - Required by a well-established 18-doctor group. Laboratory and x-ray facilities in clinic. Accredited 117-bed active treatment hospital in community of 13 000 and servicing the regional needs of 30 000 people. Camrose is a beautiful place to live, close but not too close to Edmonton, with a university, active recreational, sports and cultural programs. Contact: Mr. T.C. Ofrim, Administrator, Smith Clinic, 4825 - 51 St., Camrose, AB, Canada T4V 1R9; tel (403) 672-2424, fax (403) 679-2668. -7146

**FAMILY PRACTITIONERS, OBSTETRICIAN/GYNECOLOGISTS AND INTERNISTS: AB** - Unique practice opportunities for family practitioners, obstetrician/gynecologists and internists are available in southern Alberta. The openings are in a joint-venture clinic in Medicine Hat. This practice provides the advantages of a group setting in terms of facilities, support services and overhead sharing, as well as considerable freedom in designing the parameters of the job to fit one's own personal style. For the successful candidates, these opportunities will offer a major source of immediate referrals for the specialist, extensive walk-in services for the family doctors, superior facilities and support services with modern technology, a supportive, collegial working atmosphere within a significant medical community, immediate, very attractive earnings, a superior opportunity for achieving long-term financial security and minimal initial capital investment. These opportunities will be most attractive to family physicians with CCFP, board-certified obstetrician/gynecologists and internists who are interested in maintaining a lucrative practice with very reasonable on-call schedule, and excellent lifestyle. For more information, in complete confidence, please contact: Dr. R.W. Witzke, tel (403) 527-2281, or write 770 - 6 St. SW, Medicine Hat, AB T1A 8M7. -7119

**GENERAL PRACTITIONER: AB** - Required for May 1994, GP with operative surgical and obstetrical skills, to serve rural community of 6000 and weekend coverage of local remote solo physician communities. Contact: Dr. G.S. Nelson, tel (403) 778-2002, fax (403) 778-2127, Whitecourt. -7118

**GENERAL PRACTITIONER: AB** - We are seeking a fifth general practitioner to join two general practitioner/surgeons and two general practitioner/anesthetists in Daysland. Busy rural practice includes surgery, obstetrics, outpatient/emergency and office. New 35-bed hospital. Rotating call and vacations. Active regional medical group with CME. 1½ hours from Edmonton. Please phone or send curriculum vitae to: Daysland Medical Centre, PO Box 160, Daysland, AB T0B 1A0, tel (403) 374-3944 (bus). -7001

*Department of Pediatrics, Division of Neurology*

## Make the Commitment

B.C.'s Children's Hospital is a renowned institution committed to excellence in its care, research and teaching initiatives. This opportunity is in our Division of Neurology - Department of Pediatrics, University of British Columbia and British Columbia's Children's Hospital. This key role may develop into a tenure track position and calls for an individual who holds the Fellowship of the Royal College of Physicians and Surgeons in Neurology.

Your formal training has encompassed two years in electroencephalography reading and video/EEG monitoring and one year each in quantitative EEG modelling in epilepsy and digital EEG systems and neonatal video/EEG reading. You have previous experience in the interpretation of functional neuroimaging, such as PET, SPECT studies and Xenon-CT studies in children with epilepsy, as well as expertise in magnetoencephalography. Proven abilities in research and a solid background in teaching are essential as are strong clinical and leadership skills.

We offer a salary and benefits package that is commensurate with experience. Please forward your resume, in confidence, to: **Dr. Alan Hill, Division of Neurology, Department of Pediatrics, British Columbia's Children's Hospital, 4480 Oak Street, Vancouver, B.C. V6H 3V4.**

British Columbia's Children's Hospital

—7257

## FULL-TIME FAMILY PHYSICIANS AND SHORT-TERM LOCUMS

Queen's University Moose Factory Program

Full-time family physicians and short-term locums are required for Moose Factory General Hospital and air travel to four associated coastal communities on James Bay. Obstetrical and/or anesthesia experience desirable. Interest in teaching and cross-cultural medicine required.

Consultant back-up includes surgeon, pediatrician and anesthetist based at the hospital, regular visiting consultants in other specialties.

Competitive remuneration and benefits. In accordance with Canadian regulations, this advertisement is directed to Canadian citizens and/or permanent residents of Canada. (12-36)

For information please contact:

**Mr. Randy Kapashesit, Coordinator**
**Queen's University Moose Factory Program**
**Department of Family Medicine**
**PO Bag 8888**
**Kingston, Ontario K7L 5E9**
**Tel (705) 658-4731**
**Fax (705) 658-4057**

—7291

## ENVIRONMENTAL MEDICINE TENURE TRACK ASSISTANT/ ASSOCIATE PROFESSOR

### Department of Community Health and Epidemiology Dalhousie University Faculty of Medicine

### Director of Research, Centre for Environmental Health, Dalhousie University Faculty of Medicine

Responsibilities include:

1. To oversee research activities in a newly established clinical facility which is to provide to Nova Scotians and other Canadians validated diagnostic and treatment methods for Multiple Chemical Sensitivity and other environmentally related illnesses.
2. To conduct scientifically rigorous research in Multiple Chemical Sensitivity in collaboration with affected individuals, health care professionals, experts in building design, and research scientists. This research will emphasize studies of preventive measures and of the natural history of the various types of environmental illnesses and will include assessment of diagnostic criteria diagnostic methods and the cost effectiveness of interventions.
3. To develop research proposals in environmental medicine and obtain funding from national research agencies in support of this research.
4. To develop and teach an environmental and occupational medicine course as part of the Master of Science in the Department of Community Health and Epidemiology program at Dalhousie.
5. To direct MSc student and community medicine resident research activities in environmental medicine.
6. To participate in administrative and other departmental activities.

Qualifications:

1. Specialty certificate in occupational medicine (or equivalent) desired.
2. Training and demonstrated experience in population and clinical epidemiological studies, including clinical trials.

Other information:

Desired start-up date: July 1, 1994.

Salary based upon professional qualifications and experience.

Curriculum vitae and three references should be sent to:

**Dr. David MacLean**
**Department Head**
**Community Health and Epidemiology**
**Dalhousie University**
**Halifax, Nova Scotia B3H 4H7**
**Tel (902) 494-3860**
**Fax (902) 494-1597**

In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents.

Dalhousie University is an employment equity/affirmative action employer. The university encourages applications from qualified women, aboriginal peoples, visible minorities and persons with disabilities.

—7318

# POSITIONS VACANT

**FAMILY PHYSICIAN: AB** – To take over a well-established practice in a 17-physician multispecialty group. City population 60 000 enjoying a trade area of approximately 150 000. Candidate must have or be eligible for licensure in the province of Alberta. Position available July 1, 1994. Reply to: Dr. R.T. Garnett or Dr. P.G. Greidanus, Bigelow Fowler Clinic, 1605 - 9 Ave. S, Lethbridge, AB T1J 1W2; tel (403) 327-3121. –9902

**GENERAL PRACTITIONER: AB** – With anesthetic qualifications and obstetrical experience required for a four-physician practice to replace a departing physician. Medical staff now consists of one general surgeon and two general practitioners. A modern, fully equipped clinic is located on hospital property. The facility, a 50-bed active and 50-bed long term care complex is involved in a major capital project adding 15 long term care beds and major service areas. The town of Hanna, serving a population of approximately 8000, is located in east-central Alberta, approximately 2 hours from Calgary. Hanna has excellent educational and recreational facilities. For more information contact: Mr. Stan Faupel, Administrator, Hanna Health Care Complex, PO Box 730, Hanna, AB T0J 1P0; tel (403) 854-3331 (hospital) collect. –9873

**FAMILY PHYSICIAN: AB** – Six-doctor practice in town of 5500 (St. Paul, Alberta) 2 hours from Edmonton, requires a full-time physician with obstetrical experience. Each physician has access to the local hospital which has 55 beds including a small psychiatric unit. St. Paul is in a rural area and offers opportunities to pursue outdoor activities. Applicants should hold the LMCC and be eligible to practise in Alberta. If interested, please send a CV to: Dr. G.R. Spencer, PO Box 219, St. Paul, AB T0A 3A0; or fax to (403) 645-4566, tel (403) 645-4411. –9847

**FAMILY PHYSICIANS: AB** – Clinic facilities in community locations offering family practise with extended hours. Our company provides support staff and management. Part time or full time. Please contact: Medical Design & Management, Dr. S. Hudy, Ste. 105 131-9th Ave. SW, Calgary, AB T2P 1K1. –9830

**GENERAL PRACTITIONER: BC** – Associate family practitioner required and locum position available in a progressive, well-established six-doctor clinic in the Cariboo region of British Columbia. Accredited 60-bed acute care hospital serving an area population of 30 000 with good specialist cover. Opportunity to practise obstetrics and/or anesthesia if desired. Comprehensive family medicine, personally and financially rewarding. Remuneration is a 60/40 ratio on gross billings of approximately $150 000/annum. Evening call 1 in 15. Excellent year-round recreational facilities, both indoor and outdoor. Send resume to: Office Manager, Holley Clinic, 348 Front St., Quesnel, BC V2J 2K3; tel (604) 992-2158, fax (604) 992-9391. –7280

**FAMILY PHYSICIANS: BC** – Practices available for two family physicians with current experience in obstetrics and trauma/emergency at a five-doctor clinic in northern BC. Gross income split 60/40 initially netting annual average of $100 000+. Would be seeking 5-year minimum commitment. Qualifications for permanent registration in BC a must. Enquiries and CVs to: Executive Officer, Mountain View Medical Clinic, PO Box 456, Chetwynd, BC V0C 1J0; tel (604) 788-9617, fax (604) 788-3807. –7174

**GP ASSOCIATE: BC** – Required June 1994 to replace leaving associate in group of six. Obstetrics/anesthetics beneficial. Please contact: Dr. W.R. Mackle, Greene Clinic Associates, 501 McBride St., Prince Rupert, BC V8J 3G5; tel (604) 624-9121, fax (604) 624-9359. –7102

**FAMILY PRACTITIONER: BC** – Wanted to join three others in growing area of Victoria, BC. Excellent opportunity to relocate to the garden city. High guaranteed gross income, expenses negotiable. Reply with resume to: Box 538, CMAJ. –7041

**EXTENDED-HOUR FAMILY PRACTICES: BC** – Lower mainland, BC, full amenities. Hospital privileges/obstetrics optional, excellent call rotation. Guaranteed minimum income, dental benefits, profit sharing. Fun group. Send CV to: Dr. Turnbull, 7469 Hume Ave., Delta, BC V4G 1C3; tel (604) 946-1508. –9876

**FAMILY PHYSICIAN: NS** – Well-established, busy practice located 1 hour from Halifax in Bridgewater, Nova Scotia. Close to regional hospital, good specialist backup, good shared call-schedule. Beautiful Lahave River area, great recreation. Available June 15-30, 1994. Tel (902) 543-9925 or (902) 543-7559. –7286

**FAMILY PHYSICIAN: NS** – We're looking for an associate to replace member of five-physician group who is departing in August. Practice is located in close proximity to hospital in Shelburne, small seaport town on the beautiful south shore, 2 hours from Halifax. Practice involves shared call at hospital and obstetrics if desired. Friendly group, great recreation, challenging practice. Please contact: Dr. Gordon Hollway, tel (902) 875-2321 (bus.) or (902) 875-3256 (res.). –7093

**FAMILY PHYSICIAN: ON** – Required to join group of eight in fully equipped clinic in Whitby, Ontario. Local hospital privileges available. Rapidly growing town of 60 000. Associate initially with option for partnership. Obstetrics an asset. Write to: Dr. G.S. Burwell, 200 Brock St. N, Whitby, ON L1N 4H5; or tel (905) 668-3378. –7301

**FAMILY PHYSICIAN: ON** – Leaving practice to teach. Wonderful family practice in modern, computerized office. Plenty of pediatrics, no obstetrics. Gross income $235 000, with Wednesday afternoons off. Lab, physio and pharmacy on site. Building has one of each: ENT, opthalmologist, surgeon, cardiologist, obstetrician/gynecologist, pediatrician, as well as four other family physicians. Niagara Region offers great schools, Shaw festival and US shopping. Available to start July 5, 1994. Tel (905) 356-6195 (days) or (905) 356-5518 and leave a message. Write: c/o PO Box 59, Gp15, RR1, Niagara-on-the-Lake, ON L0S 1J0. –7278

**ASSOCIATE: ON** – Required immediately to join two family physicians in an established practice. Full or part time available. Excellent staff and fully computerized in well-organized, new office in central London. If interested please contact: Richmond Row Family Medical Centre, 615D Richmond St., London, ON N6A 3G3; tel (519) 432-4107. –7277

**FAMILY PHYSICIAN: ON** – Listowel, Ontario. Family physician required to join established practice for four. Enjoy a quality life and an exciting practice in a pleasant community. Privileges available at local 87-bed hospital. Obstetrics essential. Share call, one in ten. Please contact: Dr. A.R. Beharry, tel (519) 291-2290 or (519) 291-4324. –7327

**FAMILY PRACTICE: ON** – Associate wanted to join busy practice in Barrie, Ontario. Full or part time. Beautiful city on lake, 1 hour from Toronto, near recreational facilities. Excellent on-call schedule. Obstetrics optional. Terms flexible. Contact: Dr. Ken Seaman, 360 Bayfield St., Barrie, ON L4M 3C4; tel (705) 737-2795 (days), (705) 734-3798 (evgs.), collect. –7266

**FAMILY PRACTICE: ON** – Full-time/part-time positions available in a very busy walk-in/family practice in Brampton. Hospital privileges and obstetrics optional. Flexible hours. Gross income $275 000. Potential for partnership in a year. If interested, please call Dr. Jaya Chanchiani at (905) 452-8888. –7207

**GENERAL PRACTITIONER: ON** – One of four physicians relocating. Well-established practice in Cobourg, Ontario. Emergency shifts, obstetrics and anesthesia available. Good schools and recreational facilities. Congenial medical colleagues. Write to: Dr. Bedford-Jones, 17 Queen St., Cobourg, ON K9A 1M8; or tel (905) 372-2148. –7183

**FAMILY PHYSICIAN/GENERAL PRACTITIONER: ON** – One full-time and one part-time associate required to join busy three-doctor cottage country practice in Northbrook, Ontario, a growing area, starting preferably July 1994. No hospital work or obstetrics necessary. No call. Expenses 29%. New modern clinic. Tel: Dr. Tobia, (613) 336-8888 (days), (613) 336-9430 (after hours). –7165

**FAMILY PHYSICIAN: ON** – Required to replace retiring physician in a well-established, smaller solo practice in Kitchener, Ontario. Eight-partner call group. Reasonable rent for office and equipment. Tel (519) 743-3122, or write: Dr. G. Spackman, 1111 Union St., Kitchener, ON N2H 6J9. –7155

**FAMILY PHYSICIAN: ON** – To fill a position which has recently become available in a congenial group of six family physicians. Busy practice with a full age range of patients including nursing home coverage. Privileges at two local hospitals with full range of specialist coverage. Obstetrics optional. Emergency shifts available. Good call-schedule. Locums considered. Located in the beautiful Niagara Peninsula, 60 minutes from Toronto and 20 minutes from the United States. Excellent local recreational and cultural facilities. Send curriculum vitae to: Thorold Medical Clinic, 60 Albert St. W, Thorold, ON L2V 2G7, attn: Dr. T.R. Tatzel; or tel (905) 227-5255. –7101

# HEMATOLOGY

## FACULTY OF MEDICINE
## MEMORIAL UNIVERSITY OF NEWFOUNDLAND

Memorial University of Newfoundland, Discipline of Medicine is seeking an academic hematologist for a full-time position with the rank of Assistant Professor. This individual will also hold a joint appointment in the General Hospital, Division of Haematology.

The successful candidate will be based in the Health Sciences Centre for both academic and clinical activities and will be involved in consultation activity throughout the province. She or he will participate in undergraduate and postgraduate teaching programs and will be expected to be actively involved in clinical or laboratory research.

Candidates should hold FRCPC qualifications in internal medicine and hematology and must be eligible for full licensure in the province of Newfoundland

In accordance with Canadian immigration requirements, this advertisement is directed towards Canadian citizens, and permanent residents of Canada. Memorial University is committed to employment equity.

Please direct your application to:

**G. Adams, MD, FRCPC**
**Professor and Chief**
**Division of Haematology and Medical Oncology**
**Health Sciences Centre**
**ST. JOHN'S, Newfoundland**
**A1B 3V6**

—7319

# ANESTHETIST

Grenfell Regional Health Services requires an anesthetist based at Charles S. Curtis Memorial Hospital in St. Anthony, Newfoundland, Canada.

The Charles S. Curtis Memorial Hospital is a modern, well-equipped, 96-bed regional referral hospital, accredited by the CCHFA. The hospital provides referral and consultation services for associated Grenfell Regional Health Services hospitals, health centres and nursing stations in northern Newfoundland and Labrador. Medical services are also provided for the lower north shore of the province of Quebec and the total population served is approximately 40 000.

The workload may include visits to other hospitals in the region.

Grenfell Regional Health Services is affiliated with Memorial University, St. John's, Newfoundland and participates in the training of interns. Regular teaching sessions for junior staff and students are encouraged.

Applicants must be fellows of the Royal College of Physicians and Surgeons of Canada or hold similar standing by virtue of experience in other jurisdictions. To be eligible for registration with the Newfoundland Medical Board, graduates from medical schools outside Canada, the US, South Africa, Australia, New Zealand, Eire and Britain must have passed the Medical Council of Canada Evaluating Exam.

Fringe benefits include travel assistance to take up appointment.

Interested applicants, please apply in writing to:

**Dr. Peter J. Roberts**
**Executive Director**
**Grenfell Regional Health Services**
**St. Anthony, Newfoundland A0K 4S0**
**Tel (709) 454-3333, ext. 120**
**Fax (709) 454-2052**

—7293

# SENIOR FAMILY PHYSICIAN

## DIRECTOR OF FAMILY MEDICINE

Queen's University Moose Factory Program

Full-time senior family physician to work as the Director of Family Medicine at Moose Factory General Hospital. Interest in teaching and cross-cultural medicine is required. The Director of Family Medicine will: coordinate the family medicine clinics, ensure the quality of care of the family physician staff, provide clinical back-up for seven family physicians, organize non-surgical consultant visits, supervise the educational program for residents and clerks, provide inpatient and outpatient care, coastal visits, aeromedical evacuations, participate in hospital committees and act as liaison for the family physicians.

Consultant back-up includes surgeon, pediatrician, anesthetist based at the hospital and regular visiting consultants in other specialities.

Competitive remuneration and benefits. In accordance with Canadian regulations, this advertisement is directed to Canadian citizens and/or permanent residents of Canada. (12-36)

For further information please contact:

**Mr. Randy Kapashesit**
**Queen's University Moose Factory Program**
**Department of Family Medicine**
**220 Bagot St., PO Bag 8888**
**Kingston, Ontario K7L 5E9**
**Tel (705) 658-4731 or fax (705) 658-4057**

—7289

*Department of Pediatrics, Division of Endocrinology*

# Make the Commitment

B.C.'s Children's Hospital is a renowned institution committed to excellence in its care, research and teaching initiatives. This opportunity is in our Department of Pediatrics - Division of Endocrinology and calls for a qualified candidate at the clinical junior level. This Division serves the Province of B.C. for all tertiary care related to endocrinology disorders in infants and children.

Applicants should have a strong background in clinical or basic research, excellent teaching and clinical skills and appropriate administrative experience with proven leadership abilities.

We offer a salary and benefits package that is commensurate with experience. Please forward your resume, in confidence, to: **Dr. Wah Jun Tze, Head, Division of Endocrinology, Department of Pediatrics, British Columbia's Children's Hospital, 4480 Oak Street, Vancouver, B.C. V6H 3V4.**

IN ACCORDANCE WITH CANADIAN IMMIGRATION REQUIREMENTS, THIS ADVERTISEMENT IS DIRECTED TO CANADIAN CITIZENS AND PERMANENT RESIDENTS OF CANADA. IN ACCORDANCE WITH OUR EMPLOYMENT EQUITY PROGRAMME, WE WELCOME DIVERSITY IN THE WORKPLACE AND ENCOURAGE APPLICATIONS FROM ALL QUALIFIED CANDIDATES INCLUDING WOMEN, ABORIGINAL PEOPLES, PEOPLE WITH DISABILITIES AND VISIBLE MINORITIES.

British Columbia's Children's Hospital

—7256

# POSITIONS VACANT

**FAMILY PRACTICE: ON** – Brampton, Ontario. Busy family practice office in growing area seeking full or part-time associate. Obstetrics, emergency and other hospital work optional, but available in nearby Peel Memorial Hospital. Contact: Dr Paul Carabott, tel (905) 792-2245. -7054

**ASSOCIATE: ON** – Excellent opportunity for growth in a group practice setting in Barrie, Ontario. Cost effective overhead in a beautiful community, 1 hour from Toronto. Please call: Dr. Greg Steffens, (705) 728-5393 (days), (705) 739-8254 (evgs.) or Dr. W.L. Taylor, (705) 737-3722 (days), (705) 721-7621 (evgs.). -9903

## FAMILY PHYSICIAN
### NORTHWESTERN ONTARIO

Physician required in Nipigon, Ontario on the north shore of Lake Superior, 100 km east of Thunder Bay.

A busy family practice located in a new, modern medical clinic and hospital with hospital privileges available.

Eligible for Ministry of Health Underserviced Area Grant.

Starting date: June 1, 1994.

Please reply to:
**Dr. M.L. Jackson-Hughes**
**PO Box 279**
**Nipigon, ON P0T 2J0**
**Tel (807) 887-3836 (res.)**
**(807) 887-2992 (bus.)**
**(807) 887-3026 (hospital)** -9901

**FAMILY PRACTICE OPPORTUNITY: ON** – Opportunity to join a busy four-physician practice in a small town located on Lake Ontario, approximately 1 hour east of Toronto. Applicant should be interested in all aspects of family practice including emergency and obstetrics. Full privileges at the local hospital available. For more information contact: Cobourg Medical Centre, 68 King St. E, Cobourg, ON K9A 1L1; tel (905) 372-5494. -9898

**FAMILY PHYSICIAN: ON** – To join group practice of five family physicians in Don Mills (Toronto). Full-time position. Good diagnostic facilities. 60/40 split. Tel Dr. Fred Teixeira, (416) 429-2330. -9895

**FAMILY PHYSICIAN: ON** – For oculo-visual assessments and to treat minor eye disease. Established clinic in Kingston. Training provided. Five-day work week. No on-call. Guaranteed annual income. Incentive bonus. Future partnership or ownership potential. Confidential replies to: Box 530, CMAJ; or tel (613) 739-5603. -9884

**FAMILY PHYSICIAN: ON** – Well-established family physician requires the immediate assistance of an associate or long/short-term locum(s). My personal practice has been closed for 2 years. Due to the sudden, unexpected closure of two other practices within this community on Lake Simcoe, I am unable to accommodate an overwhelming patient load. Well-rounded family practice with an anticipated first annual gross in excess of, $150 000. We house on-site x-ray, ultrasound, a pharmacy and dentists. No obstetrics required. Please contact: Dr. P. Marchuk, PO Box 158, Pefferlaw, ON L0E 1N0; tel (705) 437-2057 (days, 9am-9pm), (705) 437-3699 (evgs., after 9pm). -9875

## MCI
## FAMILY PRACTICE MEDICAL CENTRES

MCI's reputation for high quality medical care and professionalism is unsurpassed. Build your family practice from a high-volume walk-in patient base. There are opportunities for physicians on a full or part-time basis.

### SPECIALISTS

Allergist, GP counsellor, dermatologist, gynecologist, GP psychotherapist, psychiatrist, sports medicine and surgeon required for large existing referral base.

**MCI Medical Clinics Inc.**
**40 Eglinton Ave. E.**
**Suite 802**
**Toronto, ON M4P 3A2**
**Heidi Rodriques**
**Tel (416) 440-4040, ext. 425** -9825

**FAMILY PHYSICIANS: ON** – Don't miss this opportunity to practise family medicine as it was meant to be. We are looking for family physicians with or without anesthesia to join a congenial group of seven physicians in a newly constructed state-of-the-art clinic adjacent to a fully accredited hospital. Dryden has been designated underserviced for a GP/anesthetist. Located in beautiful northwestern Ontario, Dryden is situated on Wabigoon Lake. It is a progressive community of 6500 (service area of 16 000) with excellent educational and recreational facilities. For further information contact: Dr. Mark Dahmer at (807) 223-4202 (after office hours), or Nancy Pentney at (807) 223-2260 (during office hours); or write the Dingwall Medical Group, PO Box 3011, Dryden, ON P8N 2Z6; fax (807) 223-4733. -9817

## MEDVISIT
Doctor's Housecall Service Inc.

**PHYSICIANS REQUIRED FOR HOUSECALLS GREATER METRO TORONTO AREA**

- Very low overhead of 10-15%
- Part/full time - day or evening - no overnight call
- Free alphanumeric paging
- Introductory shifts without charge or obligation

**CONTACT: Dr. TOM BURKO, (416) 631-0298**
(For opportunities in Ottawa call (613) 564-6767.) -9696

**FULL OR PART-TIME ASSOCIATE: SK** – Extended-hour family practice. New clinic in rapidly expanding northwest Regina. Clinic open 9 am to 9 pm, 7 days per week. This clinic is located very close to busy shopping mall, school, library and sports complex. Seeking full or part-time associate. Please contact: Dr. V. Gomes, tel (306) 543-0770 or fax (306) 543-7766. -7303

**FULL SCOPE FAMILY PRACTICE PLUS OBSTETRICS: IOWA, US** – A $175 000 package in northern Iowa's playground (fishing and hunting). Fine restaurants and university performing arts centre all within 20 minutes of your office. Please call Bill Ritchie of Harris Kovacs Alderman at (800) 776-7901, ext. 3-346, or fax your CV to (800) 248-8533. LMCC approved state. -7285

## FAMILY PHYSICIANS

Northern Medical Services, University of Saskatchewan has salaried positions available in remote areas of northern Saskatchewan. Health care is delivered from modern facilities by teams of physicians, nurses, community health care representatives and visiting consultants.
Salary range: $97 617-$114 699 per annum. Additional benefits: subsidized modern furnished housing and utilities; transportation expenses; and paid leave for 4 weeks of vacation, 4 weeks of continuing education and two conferences per year.
To apply, or for further information contact:

**Wayne Nelson, Administrative Officer**
**Northern Medical Services**
**202, 308 - 4th Ave. N.**
**Saskatoon, SK S7K 2L7**
**Fax (306) 665-6077** -9714

**FAMILY PRACTICE OPPORTUNITY: KANSAS, US** – Rural hospital and healthcare centre in pleasant country setting requires additional practitioner. Obstetrics would be an asset. Easy drive to Colorado mountains or major cities. Above average earnings guaranteed with many other benefits. Hospital will look after immigration and relocation details. This is not an agency. Call Canadian physician for more information, tel (902) 434-4704; or call administrator, tel (316) 659-3621 (collect). -7310

**BC/BE FAMILY PRACTITIONERS: MICHIGAN, US** – Two-physician, single-specialty group in Jackson, Michigan, expanding to primary care multispecialty group, is seeking BC/BE family practitioners. Busy practice, one-in-seven call, no obstetrics. Competitive income guarantee plus productivity incentive. Student loan forgiveness. Partnership opportunity. Affiliation with 494-bed, state-of-the-art hospital built in 1983 featuring Level II nursery and 210+ medical staff. Area offers great family lifestyle; features include 150 lakes, 18 golf courses, theatre and museums. Housing rated most affordable in the country by National Home Builder's Association. Conveniently located 48 km from Ann Arbor and Lansing. Call: Kim Keller, (800) 894-2694, Physician Recruiter, W.A. Foote Memorial Hospital. -7281

**TWO-PERSON MEDICAL TEAM: NEPAL** – Sir Edmund Hillary Foundation; two-person medical team required for 2 years starting January 1995, Khunde Hospital (nine beds), Mt. Everest area; 12 500 ft. elevation. Population Sherpa and Nepalese. Responsible for medical and emergency problems, training and supervising local health workers, and health education. Further information, contact: Dr. Joan Ford, 544 Richmond St., New Westminster, BC V3L 4C7. -7282

**DIRECTOR, INTENSIVE CARE UNIT: BC** – St. Paul's Hospital, University of British Columbia, is searching for an outstanding academic intensivist to serve as director of the ICU, to lead the ICU to international stature in its clinical, teaching, and research programs. St. Paul's Hospital is a 560-bed tertiary care teaching hospital located in downtown Vancouver and affiliated with the University of British Columbia. The growth and development of critical care medicine is one of the major strategic goals of St. Paul's Hospital. The ICU is a 14-bed medical/surgical ICU with about 750 admissions per year. The ICU is staffed by four academic intensivists, CCM fellows, residents and interns. St. Paul's Hospital is a major site of teaching in a Royal College of Physicians and Surgeons of Canada accredited fellowship training program

in CCM. There are very active basic science and clinical research programs. We are seeking an experienced intensivist who has demonstrated leadership capabilities in clinical care, teaching, and research and who has basic specialty certification in anesthesia, medicine or surgery. The director of the ICU will have a full-time tenure track (grant) appointment at the University of British Columbia. Academic rank and salary will be commensurate with qualifications and experience. Start date - July 1, 1994. Please submit a letter of application, a CV, and the names of three referees, by May 15, 1994, to: James Russell, MD, Chair, Search Committee for Director of ICU, St. Paul's Hospital, 1081 Burrard St., Vancouver, BC V6Z 1Y6. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. SPH/UBC welcomes all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. -7169

**GENERAL INTERNIST: ON** – For Dryden and area, population 20 000. Accredited hospital, newly constructed, well-equipped office. New cardiac stress testing and endoscopy equipment available. Fashion practice to your lifestyle and enjoy all that northwestern Ontario has to offer. Possible underserviced area incentive grant. Contact: Nancy Pentney, tel (807) 223-2260, or Dr. Mark Dahmer, tel (807) 223-4202 (after hours). -9867

FRASER-BURRARD
Hospital Society

**Pediatrician - Neonatologist**

Applications are invited from pediatricians with expertise/special interest in Neonatology, with Canadian fellowship qualifications and eligible for licensure in British Columbia. Preference will be given to those candidates with special training in Neonatology.

The Fraser-Burrard Hospital Society (Royal Columbian Hospital, 400 bed major referral and teaching centre and Eagle Ridge Hospital, 150 bed community hospital) serves a community of approximately 140,000 people and a catchment area of 200,000. The Royal Columbian Hospital has 3,000 births annually and a 28 bed special care nursery with Level 3 status. The hospitals are located in New Westminster and Port Moody, just 20 minutes by rapid transit or freeway to downtown Vancouver and close to multi-recreational areas.

Applications **must be received by 31 July 1994**. Direct inquiries with a curriculum vitae to:
**Dr. R.C. MacPherson**
**Vice President, Medicine**
**The Fraser-Burrard Hospital Society**
**260 Sherbrooke Street**
**New Westminster, B.C. V3L 3M2** —7322

**INTERNAL MEDICINE**
**PHYSICIAN**

Outstanding opportunity in the United States to establish a practice in internal medicine in a pleasant community in central New York. BC/BE physician will be on the medical staff of a well-equipped, progressive, 67-bed, modern hospital in Fulton, New York, 32 km north of Syracuse. The community provides excellent family lifestyle environment and school system, four-season recreational area and is near cultural activities and colleges. Excellent startup package available including immigration fees.
Send CV to:
**Dennis Casey, Executive Director**
**A.L. LEE MEMORIAL HOSPITAL**
**510 S Fourth St.**
**Fulton, NY 13069**
**Tel (315) 592-2224, ext. 121**
**Fax (315) 593-1159** -7298

**PEDIATRIC NEPHROLOGIST: BC** – The Division of Nephrology, Department of Pediatrics, University of British Columbia at British Columbia's Children's Hospital, Vancouver is seeking a qualified pediatric nephrologist at the assistant professor level. This is a grant tenure track position. Requirements will include consultative research, teaching and service duties primarily with British Columbia's Children's Hospital. Candidates will be required to devote at least 50% of their time in establishing a successful laboratory and clinical research program in pediatric nephrology, therefore prior training and experience in research methodology is necessary. Candidate should also show evidence of experience in teaching and clinical care. The successful candidate will have completed the specialist training requirements of the Royal College of Physicians and Surgeons of Canada in pediatric nephrology and will be expected to successfully complete the Royal College examinations in pediatrics and pediatric nephrology. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Salary will be commensurate with qualifications and experience. UBC welcomes all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. Anticipated start date is July 1, 1994. Please reply with an up-to-date curriculum vitae, before June 1, 1994, to: Dr. Judith G. Hall, Head, Division of Nephrology, British Columbia's Children's Hospital, 4480 Oak St., Vancouver, BC, Canada V6H 3V4. -7234

**OBSTETRICIAN/GYNECOLOGIST: AB** – Required by a well-established 18-doctor group. Laboratory and x-ray facilities in clinic. Accredited 117-bed active treatment hospital in community of 13 000 and servicing the regional needs of 30 000 people. Camrose is a beautiful place to live, close but not too close to Edmonton, with a university, active recreational, sports and cultural programs. Contact: Mr. T.C. Ofrim, Administrator, Smith Clinic, 4825 - 51 St., Camrose, AB Canada T4V 1R9; tel (403) 672-2424, fax (403) 679-2668. -7148

**ANATOMICAL PATHOLOGIST: BC** – The Department of Pathology and Laboratory Medicine, University of British Columbia, and St. Paul's Hospital invite applications by qualified anatomical pathologists for an (grant tenure track) assistant professor position. Preference may be given to those individuals with particular interests in immunopathology, gastrointestinal pathology, or endocrine pathology. The successful applicant must have exceptional anatomical skills, an emerging track record of scholarly accomplishment, a commitment to scholarship, and strong educational ability for large and small groups. Skills in biotechnological applications to pathological diagnosis are desirable. Responsibilities include surgical pathology, subspecialty anatomic pathology if appropriate to the applicant's abilities and interests, rotations on the autopsy pathology service, clinical and classroom teaching, and scholarship in modern anatomic pathology. Salary will be commensurate with qualifications and experience. The position is offered in the context of a progressive, busy, multi-site department in a major tertiary-quaternary teaching hospital (St. Paul's) of the University of British Columbia. The faculty in the Department of Pathology and Laboratory Medicine is committed to excellence in all service, educational and investigative domains of the discipline. There is strong inter-site interaction, and a superb residency program. The University of British Columbia welcomes all qualified applicants, especially women, aboriginal people, visible minorities, and persons with disabilities. In accordance with Canadian immigration requirments, this advertisement is directed to Canadian citizens and permanent residents. Deadline for application is May 15, 1994 with a starting date of July 1, 1994. Interested individuals should send their curriculum vitae, along with the names and addresses of three referees and a brief prospectus of one's professional goals, to: Bruce McManus, MD, PhD, Professor and Head, Department of Pathology and Laboratory Medicine, University of B.C., 2211 Westbrook Mall, Vancouver, BC C6T 2B5. -7237

**PEDIATRICIAN**
**NORTH CAROLINA**

Tired of government interference and cold weather? Follow fellow Canadian MDs (obstetricians) to North Carolina. Opportunity for one or two BE/BC pediatricians to join existing pediatrician or establish new practice. Beautiful new birthing centre with growing obstetrical/neonatal service. Nice community located close to larger city. Many recreational opportunities. Income guarantee, benefits, and other incentives negotiable. Videotape available.

Contact:
**Robert Enders, President**
**Morehead Memorial Hospital**
**117 E Kings Hwy.**
**Eden, NC 27288**
**Tel (800) 944-8230.** -7300

**RADIOLOGIST: ON** – Position available in a well-established practice in the Kitchener-Waterloo area (southwestern Ontario). General radiology, mammography, ultrasound and nuclear medicine. Please reply with CV to: Diagnostic Imaging Associates, attn.: A. Marshall, 366-1720 Howard Ave., Windsor, ON N8X 5A6. -9891

**SUBSPECIALIST IN REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY: BC** – The Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynaecology, the University of British Columbia, is seeking a clinical subspecialist in reproductive endocrinology and infertility to play a major role in patient care, clinical research and teaching. The appointee will join the division's five geographic full-time clinical and three basic scientist members, with a start date of July 1, 1994. Specific responsibilities: full participation in the division's programs, including in vitro fertilization, ovulation induction, therapeutic donor insemination and gynecologic ultrasound scanning; comprehensive consultation and clinical care of patients

## Attention Orthopedic Surgeons. . .

**THE OPPORTUNITY**
York Central Hospital, a progressive and modern 247-bed community hospital, serving one of Canada's fastest demographic growth areas, is seeking a third orthopedic surgeon for its busy orthopedic service.

**THE REQUIREMENTS**
**The candidate should be a Canadian certified, Ontario licensed, recent graduate in orthopedic surgery.** Qualifications also include a broad interest in orthopedics; a willingness to participate in cross-coverage with a neighbouring hospital; a customer service focus.

**THE BENEFITS**
In addition to being part of a busy, progressive, customer service oriented team, the candidate will be associated with a well-managed, community hospital known for its focus in the following program areas: surgical (including orthopedics); emergency medicine; medicine; long term care; mental health; woman and child.

York Central Hospital, located in Richmond Hill, offers the benefits of a well-established community, combined with the availability of excellent recreational and educational facilities and easy access to Toronto.

For more information about the opportunity, requirements or benefits, please contact: Dr. Chris Watson, Section Head, Orthopaedics, tel (905) 883-1497, by June 30, 1994:

**Dr. C. Watson**
**Section Head, Orthopaedics**
**York Central Hospital**
**10 Trench Street**
**Richmond Hill, Ontario**
**L4C 4Z3**

—7317

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Plummer Memorial Public Hospital

Sault Ste. Marie General Hospital

## RADIOLOGIST ONTARIO

Sault Ste. Marie General and Plummer Memorial Hospitals require a full-time radiologist with FRCPC and Ontario licence or eligibility for same. This position is expected to be exempt from forthcoming billing number restrictions. The successful candidate must be experienced in general angiography and interventional procedures. The hospital practice includes all modalities except MRI. A third colour doppler ultrasound unit will soon be purchased, and CT (already 3D capable) will be upgraded to spiral status in the near future. A new state-of-the-art digital/angiography suite is in the planning stages and is scheduled to be completed by the fall. An opportunity to participate in a busy private clinic practice is presently being negotiated.

The newly amalgamated, fully accredited hospitals are under new administration and service a city population of 80 000 and catchment area of 110 000, with a total of 400 beds. This career opportunity offers excellent remuneration, and is eligible for a tax free grant from the Underserviced Area Program.

Please submit current CV and three references, in complete confidence, to:

**Dr. David Stenning, Chief**
**Department of Diagnostic Imaging**
**Sault Ste. Marie General Hospital**
**941 Queen St. East**
**Sault Ste. Marie, Ontario P6A 2B8**

—7292

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## GENERAL SURGEON

Queen's University Moose Factory Program

Queen's University requires a general surgeon for the Queen's University-Moose Factory Program in northeastern Ontario, Canada. This is a unique opportunity to provide general surgery services to a predominantly Cree Indian population in the eastern James and Hudson Bay lowlands.

The Moose Factory General Hospital is a 58-bed accredited facility. Opportunity to be involved in teaching surgical residents and to practise cross-cultural medicine. Academic appointment, competitive remuneration and benefits and housing provided. In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada.

For more information contact:

**Mr. Randy Kapashesit**
**Coordinator, Moose Factory Program**
**Tel (705) 658-4731, fax (705) 658-4057**

For further specific enquiries contact:

**Dr. George Wolfe**
**Surgeon**
**Moose Factory**
**Tel (705) 658-4544**

Send curriculum vitae to:

**Moose Factory Program**
**Department of Family Medicine**
**220 Bagot St., PO Bag 8888**
**Kingston, Ontario K7L 5E9**
**Fax (613) 544-9899**

—7290

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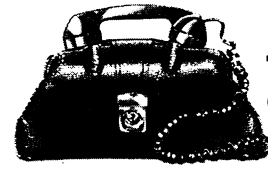

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with reproductive endocrine and infertility problems; research encompassing in vitro fertilization and related areas of reproductive endocrinology and infertility and participation in undergraduate and postgraduate teaching programs. Qualifications: demonstrated abilities in teaching, independent and collaborative clinical research, a keen interest in working in an academic environment and in the areas of assisted reproduction noted, eligibility of licensure with the College of Physicians and Surgeons of British Columbia, FRCSC in obstetrics and gynecology and completion of at least 2 years of recognized North American fellowship training or equivalent in the subspecialty of reproductive endocrinology and infertility and satisfactory achievements for appointment to the clinical staff of the Department of Obstetrics and Gynecology, Vancouver General Hospital, and the Faculty of Medicine, University of British Columbia. This 1-year renewable appointment will be at the clinical assistant or clinical associate professor level depending on the experience and qualifications of the candidate. In accordance with Canadian immigration and employment requirements, priority will be given to Canadian citizens and permanent residents of Canada. The University of British Columbia welcomes all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. Please submit your curriculum vitae to: Dr. Basil Ho Yuen, Head, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of British Columbia, 4490 Oak St., Vancouver, BC V6H 3V5. The closing date for applications is June 1, 1994. -7236

**RESPIROLOGIST: BC** - Twenty minutes from downtown Vancouver, close to the finest recreational areas in Canada. Join a group of six respirologists practising out of two referral hospitals and two community hospitals (bed base in excess of 1000 and referral area in excess of 500 000). Practice includes office and hospital consultations, diagnostic services (including three bronchoscopy services, three pulmonary function labs, exercise laboratory, inhalation challenge laboratory), therapeutic services (including respiratory rehab program, asthma clinic, transtracheal oxygen clinic, inpatient respiratory unit) and clinical investigation units in two hospitals. Experience in critical care medicine essential since work involves participation in ICU in two separate referral/teaching hospitals. Busy and highly remunerative practice. Candidates will be requested to do a locum period prior to being considered for this position. Investment required. This position may not be affected by recent reduction in fee schedule for out-of-province physicians. Please reply to: Box 553, CMAJ. -7270

**RHEUMATOLOGIST: ON** - Peel Memorial Hospital has an immediate requirement for a dual-certified internist. The successful candidate will be required to rotate through the internal medicine call-schedule including ICU coverage. The major focus for the rheumatology specialty will be on outpatient/office care. Peel Memorial Hospital is a busy 422-bed community hospital situated in Brampton, approximately 35 minutes from Toronto. Please send enquiries and curriculum vitae to: Dr. David Borts, Chief, Department of Internal Medicine, Peel Memorial Hospital, 20 Lynch St., Brampton, ON L6W 2Z8. -7312

**GENERAL SURGEON: MB** - Required for a town in southern Manitoba with a population of 2500, with an approximate catchment area of 30 000. Located 75 km from Winnipeg in central region of approximately 95 000 and offers excellent recreational services and a consolidated elementary/high school. Fully accredited 30-bed acute care hospital with well-established practice; laparoscopic/endoscopic equipment and visiting radiologist and internist. Ability to do gynecology/orthopedics an asset. Opportunity to do surgery in other facilities in this region on an outreach basis also available. Position open as of Mar. 30, 1994. Contact: Dr. Mike Omichinski, Carman Medical Group, tel (204) 745-2024, or Mr. Rene Comte, Executive Director, Carman Hospital, tel (204) 745-2021; or fax (204) 745-2756; or apply in writing to above at: Carman Memorial Hospital, PO Box 610, Carman, MB R0G 0J0. -7184

## GENERAL SURGEON

The County of Bruce General Hospital, a fully-accredited, community hospital, located in Walkerton, Ontario, 96 km north of Kitchener-Waterloo, is currently searching for a general surgeon to serve a community of approximately 15 000. Ideally, the candidate will have experience in orthopedics and laproscopic skills in order to step into a busy, existing practice.

Interested applicants should direct enquiries to:

**Guy Kirvan, Executive Director**
**County of Bruce General Hospital**
**21 McGivern St.**
**Walkerton, ON N0G 2V0**
**Tel (519) 881-1220, ext. 220, or**
**Dr. Frank MacNiven**
**County of Bruce General Hospital**
**Tel (519) 881-1220, ext. 363** -7275

**GENERAL SURGEON: SK** - Required for prosperous community in west central Saskatchewan with a drawing area of 16 000. Apply to: Kindersley Clinic, PO Box 1390, Kindersley, SK S0L 1S0; or call Dr. Dan Johnson at (306) 463-2621. -7225

**ORTHOPEDIC SURGEON: ON** - Required to replace incumbent leaving for the US. Small friendly hospital with a catchment area of 30 000 +. Good facilities. Call: Dr. G.E.R. Vaughan, (519) 627-3531 (bus.), (519) 627-8443 (res.); or write: Box 547, CMAJ. -7161

**GENERAL SURGEON: ON** - For community of 6500 in northwestern Ontario. Service area of 12 000. Fully accredited 67-bed hospital with 37 acute care beds. Support from general internist and 14 family physicians on medical staff. Excellent recreational area for hunting, fishing, camping, etc. Progressive, stable community. For enquiries contact: Dr. C.J. Eisener, Chief of Staff, Dryden District General Hospital, PO Box 3003, Dryden, ON P8N 2Z6; tel (807) 223-5261, fax (807) 223-2370. -7036

**DIRECTOR, TRAUMA SERVICES: BC** - The position of Director, Trauma Services at the Vancouver Hospital and Health Sciences Centre (VHHSC) will become available July 1, 1994. The VHHSC is a 900-bed university tertiary referral and trauma centre for the province of British Columbia. VHHSC is the provincial centre for burns and spinal cord injuries. Over 2200 trauma patients are admitted annually (400 with injury severity score $\geq$ 16). The VHHSC is currently seeking an FRCSC physician/surgeon with formal postgraduate trauma training. The individual selected will be expected to take a leadership role in all aspects of interdisciplinary trauma care. Administrative duties will include responsibility for the provincial trauma registry, provincial trauma hotline and community outreach programs. This position affords an opportunity for a full-time grant tenure track university appointment in the Department of Surgery, Faculty of Medicine, The University of British Columbia, at the level of assistant or associate professor as appropriate. Academic responsibilities include undergraduate and postgraduate teaching and research. Salary will be commensurate with qualifications and experience. The University of British Columbia welcomes all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Interested applicants should submit a curriculum vitae by May 15, 1994, to: Alex Berland, Vice President, Clinical Services, Vancouver Hospital and Health Sciences Centre, 855 W 12th Ave., Vancouver, BC, Canada V5Z 1M9. -7168

**UROLOGIST: AB** - Required by a well-established 18-doctor group. Laboratory and x-ray facilities in clinic. Accredited 117-bed active treatment hospital in community of 13 000 and servicing the regional needs of 30 000 people. Camrose is a beautiful place to live, close but not too close to Edmonton, with a university, active recreational, sports and cultural programs. Contact: Mr. T.C. Ofrim, Administrator, Smith Clinic, 4825 - 51 St., Camrose, AB Canada T4V 1R9; tel (403) 672-2424, fax (403) 679-2668. -7147

## POSITIONS WANTED

**FEMALE FAMILY PHYSICIAN: AB** - Seeking associateship in Calgary. CCFP, ACLS, ATLS. Interested in obstetrics. Hospital privileges desired. Please call Dr. Christin Hilbert at (905) 577-0047 and leave a message. -7125

**GP/SURGEON: ON** - GP/surgeon will do obstetrics for small community hospital in Ontario. Reply to: Box 557, CMAJ. -7313

**GASTROENTEROLOGIST: ON** - Wishing to purchase practice (in full or to share) in Toronto area. Reply to: Box 550, CMAJ. -7223

**RADIOLOGIST: ON** - DABR, FRCPC with extensive experience and proven expertise in CT, ultrasonography, nuclear medicine, interventional procedures and angiography, neuroradiology and every area of general radiology including mammography, seeks practice opportunities in Ontario, preferably in the metropolitan Toronto region. Please respond at the earliest to: Box 546, CMAJ. -7139

## PRACTICES FOR SALE

**DERMATOLOGY PRACTICE: AB** - Well-established solo dermatology practice for sale. Computerized, ultraviolet unit. Priced to sell quickly. Reply to: Box 559, CMAJ. -7325

**DERMATOLOGY: AB** – Red Deer, Alberta. Clean, safe college city of 60 000, draws on 200 000 population. Regional hospital with full facilities. Practice is unopposed. Fully equipped office available. Incumbent will introduce. Contact: tel (403) 347-1933, or Box 543, CMAJ. –7099

**FAMILY PRACTICE: AB** – Well-established, rapidly expanding, residential community primary care office in southeast Calgary. Well-appointed two-physician facility with private in-house laboratory associated with community dentist and pharmacy. Contact: Dr. Norris W. Rich, CCFP, 652 Lake Moraine Way SE, Calgary, AB T2J 3A5; tel (403) 278-4167. –7217

**GENERAL MEDICINE PRACTICES AVAILABLE: BC** – Various attractive locations. Financing available. For details (without charge) contact in confidence: Malcolm McIntosh, Medical Management Consultant, 2275 Brighton Ave., Victoria, BC V8S 2G1; tel (604) 380-8005 (24 hours). Serving Canadian physicians since 1960. –7079

**FAMILY PRACTICE: BC** – Well-established busy family practice in Surrey, located 1 block from 534-bed Surrey Memorial Hospital. Near lab and x-ray clinics. Good lease. Contact: Dr. J. Stipec, 7-13665-96 Ave., Surrey, BC V3V 1Z1; tel (604) 581-6176. –9881

**FAMILY PRACTICE: BC** – Well-established solo family practice in Vancouver, BC. Excellent location in medical building with lab and x-ray. Leased premises with option to purchase building shares. Obstetrics as desired. Incumbent retiring. Reply to: PO Box 91857, West Vancouver, BC V7V 4S1; fax (604) 922-3582. –9899

**PRACTICE FOR SALE: BC** – Vancouver. Female physician wishes to relocate in December. Very low price, excellent location, new office, congenial call group. Obstetrics necessary. Tel (604) 687-1330 (days), or (604) 684-1140 (evgs.). –9889

**FAMILY PRACTICE: NS** – Family practice in small town with easy access to Halifax. Reply to: Box 556, CMAJ. –7302

**FAMILY PRACTICE: ON** – West-end Ottawa. Well-established, busy practice. List about 4000. Shared overhead. Computerized billing. Fully equipped with on-site laboratory. Complete night, weekend and holiday coverage. Incumbent retiring end of 1994. Will personally introduce successor to patients. Reply to: Box 554, CMAJ. –7273

**SOLO GENERAL PRACTICE: ON** – Stratford, Ontario. Established 23 years. Excellent rota. Hospital privileges available. Reply to: 386 Cambria St., Stratford, ON N5A 1J4; tel (519) 271-6803. –7227

**FAMILY PRACTICE: ON** – Excellent opportunity to join well-established family practice of nine associates in Kingston, Ontario. Female physician relocating. Obstetrics optional. Terms negotiable. Available January 1995. Contact: Ellen Turcotte, Clinic Manager, tel (613) 544-8383, fax (613) 544-7247. –7222

**FAMILY PRACTICE: ON** – Well-established family practice for sale in southwestern Ontario, within commuting distance of London and Kitchener. Excellent on-call; obstetrics optional. Grossing in excess of $300 000 per year. Contact: Michael Bondy, BA, CA, Kime, Mills, Dunlop, tel (519) 679-8550. –7219

**FAMILY PRACTICE: ON** – Midtown Toronto location, busy family practice in high density area. Available December 1993. No on call, no obstetrics, no hospital privileges. Can be expanded. Terms available. Tel (416) 485-5361. –7088

**INTERNAL MEDICINE: ON** – Enjoyable and very lucrative internal medicine practice for sale. Community just west of the Toronto area. Please address enquiries to: Box 558, CMAJ. –7324

**ESTABLISHED OBSTETRICS/GYNECOLOGY PRACTICE: ON** – Well-established obstetrics/gynecology practice including ultrasound, colposcopy and building; 1 block from St. Joseph's Hospital, Hamilton, Ontario. Contact: Dr. Frank Krar, tel (905) 525-2251, fax (905) 523-9988. –7267

**OPHTHALMOLOGY PRACTICE: ON** – Well-established, mostly primary care, with a very large dispensing division, with trained staff and part-time permanent locum tenens associates, in the Toronto area. Owner relocating. Reply: PO Box 278, Stn. T, Toronto, ON M6B 4A1. –7096

## PRACTICES FOR SALE

**ESTABLISHED PRACTICE: IDAHO, US** – Suitable for primary care physician. Office in residential area of Coeur d'Alene, Idaho, 4 blocks from lake, 5 minutes from splendid community hospital with MRI, CT, laboratory. All specialties covered. Mild winters, gorgeous summers. Great place to raise a family. Reply to: E.R.W. Fox, MD, 1401 E Lakeshore Dr., Coeur d'Alene, ID 83814. –7274

## PRACTICES WANTED

**RADIOLOGY CLINICS: ON** – Greater Toronto region x-ray and ultrasound clinics are sought to provide professional radiological services at competitive rates. Negotiable terms for service contracts, equity share and/or goodwill purchase. Please reply in strictest confidence to: Box 548, CMAJ. –7192

**CLINICS: ON** – X-ray and/or ultrasound clinic(s) to purchase in metropolitan Toronto area. Reply to: Box 215, CMAJ. –9860

## VACATIONS

**NAHANNI:** – River of dreams, river of gold. We offer adventures for beginners and experts alike through this land of legend, myth and romance. All trips experience Virginia Falls (twice the height of Niagara), Canada's deepest river canyons, hot springs and unique geological features. Nahanni River Adventures, PO Box 4869M, Whitehorse, YT Y1A 4N6; tel (403) 668-3180, fax (403) 668-3056. –7248



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## INDEX DES ANNONCEURS






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# ISOPTIN® SR

VERAPAMIL HYDROCHLORIDE SUSTAINED-RELEASE TABLETS

## ONE DRUG. ONCE A DAY.

**THERAPEUTIC CLASSIFICATION: Antihypertensive**

**INDICATIONS: ISOPTIN Sustained Release (SR) Tablets:** ISOPTIN-SR is indicated in the treatment of mild to moderate essential hypertension. ISOPTIN-SR should normally be used in those patients in whom treatment with diuretics or beta blockers has been associated with unacceptable adverse effects. ISOPTIN-SR can be tried as an initial agent in those patients in whom the use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of ISOPTIN-SR with a diuretic has been found to be compatible and showed additive antihypertensive effect. ISOPTIN-SR should not be used concurrently with beta blockers in the treatment of hypertension (See DRUG INTERACTIONS). Safety of concurrent use of ISOPTIN-SR with other antihypertensive agents has not been established and such use cannot be recommended at this time.

**CONTRAINDICATIONS:** 1. Acute myocardial infarction. 2. Severe congestive heart failure and/or severe left ventricular dysfunction (unless secondary to a supraventricular tachycardia amenable to oral verapamil therapy). 3. Cardiogenic shock. 4. Severe hypotension. 5. Second- or third-degree A-V block. 6. Sick sinus syndrome (See WARNINGS). 7. Marked bradycardia. 8. Hypersensitivity to the drug. 9. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Ganong-Levine syndromes)(See WARNINGS).

**WARNINGS:** Because of the drug's negative inotropic effect, verapamil hydrochloride should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by a dysrhythmia. If verapamil is used in such patients, they must be digitalized prior to treatment. It has been reported that digoxin plasma levels may increase with chronic verapamil administration (See DRUG INTERACTIONS). The use of verapamil in the treatment of hypertension is not recommended in patients with heart failure caused by systolic dysfunction. Hypotensive symptoms of lethargy and weakness with faintness have been reported following single oral doses and even after some months of treatment. In some patients it may be necessary to reduce the dose. In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of verapamil should be taken into consideration. Verapamil slows conduction across the A-V node and rarely may produce second or third degree A-V block, bradycardia and in extreme cases, asystole. Verapamil causes dose-related suppression of the S-A node. In some patients, sinus bradycardia may occur, especially in patients with a sick sinus syndrome (S-A nodal disease), which is more common in older patients (See CONTRAINDICATIONS). The total incidence of bradycardia (ventricular rate less than 50 beats/min) was 1.4% in controlled studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to A-V nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately. Verapamil may result in significant acceleration of ventricular response during atrial fibrillation or atrial flutter in the Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine syndromes after receiving intravenous verapamil. Although a risk of this occurring with oral verapamil has not been established, such patients receiving verapamil may be at risk and its use in these patients is contraindicated (See CONTRAINDICATIONS). Generally, oral verapamil should not be given to patients receiving beta blockers since the depressant effects on myocardial contractility heart rate and A-V conduction may be additive. However, in exceptional cases when in the opinion of the physician concomitant use in angina and arrhythmias is considered essential, such use should be instituted gradually under careful supervision. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed. Verapamil gives no protection against the dangers of abrupt beta blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta blocker. Then verapamil may be started with the usual dose. **Patients with Hypertrophic Cardiomyopathy:** In 120 patients with hypertrophic cardiomyopathy who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects was seen. Three patients died in pulmonary edema: all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension, abnormally high (greater than 20 mm Hg) pulmonary wedge pressure and a marked left ventricular outflow obstruction was present in most of these patients. Concomitant administration of quinidine (See DRUG INTERACTIONS) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree A-V block in 4% and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction but in some cases, verapamil use had to be discontinued. **Elevated Liver Enzymes:** Elevation of transaminase with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Several published cases of hepatocellular injury produced by verapamil have been proven by rechallenge. Clinical symptoms of malaise, fever, and/or right upper quadrant pain, in addition to elevation of SGOT, SGPT and alkaline phosphatase have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent. **Hepatic Insufficiency:** Because verapamil is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function, since the elimination half-life of verapamil in these patients is prolonged 4-fold (from 3.7 to 14.2 hours). A decreased dosage should be used in patients with hepatic insufficiency and careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect should be carried out (See PHARMACOKINETICS and DOSAGE AND ADMINISTRATION). **Renal Insufficiency:** About 70% of an administered dose of verapamil is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil was 12.08 mL/min/kg, while in patients with advanced renal disease it was reduced to 5.33 mL/min/kg. This pharmacokinetic finding suggests that renal clearance of verapamil in patients with renal disease is decreased. In two studies with oral verapamil, no difference in pharmacokinetics could be demonstrated. Therefore, until further data are available, verapamil should be used with caution in patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect (See DOSAGE AND ADMINISTRATION).

**PRECAUTIONS:** Atypical lens changes and cataracts were observed in beagle dog studies at high doses. This has been concluded to be species-specific for the beagle dog. (These ophthalmological changes were not seen in a second study.) No similar changes have been observed in long-term prospective human ophthalmological trials. Verapamil does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may decrease the therapeutic effect of verapamil. **Use in Patients With Attenuated (Decreased) Neuromuscular Transmission:** It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vercuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission. **Use in The Elderly:** Caution should be exercised when verapamil is administered to elderly patients (≥65 years) especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency. The incidence of adverse reactions is approximately 4% higher in the elderly. The adverse reactions occurring more frequently include dizziness and constipation. **Pregnancy:** Teratology and reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity or impaired fertility. In rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no studies in pregnant women. However, verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. ISOPTIN is not recommended for use in pregnant women unless the potential benefits outweigh potential risks to mother and fetus. **Labor and delivery:** It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. **Nursing mothers:** Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered. **Use in Children:** The safety and dosage regimen of verapamil in children has not yet been established.

**DRUG INTERACTIONS: Beta-adrenergic Blockers:** The concomitant administration of verapamil with beta-blockers can result in severe adverse effects (See WARNINGS). **Digoxin:** Verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29% respectively. Maintenance and digitalization doses should be reduced when verapamil is administered and the patient should be reassessed to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization. **Antihypertensive Agents:** Verapamil administered concomitantly with other antihypertensive agents may have an additive effect on lowering blood pressure. In patients with angina or arrhythmias using antihypertensive drugs, this additional hypotensive effect should be taken into consideration. In patients with hypertension, combination with a diuretic has been found to be compatible; however, combination with other antihypertensive agents has not been established. Verapamil should not be combined with beta blockers for the treatment of hypertension. **Antiarrhythmic Agents: Quinidine:** In a small number of patients with hypertrophic cardiomyopathy, concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided. The electrophysiologic effects of quinidine and verapamil on A-V conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on A-V conduction. There has been a report of increased quinidine levels during verapamil therapy. **Disopyramide:** Until data on possible interactions between verapamil and disopyramide are obtained,disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration. **Flecainide:** A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction. **Other: Nitrates, Diuretics:** No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil. **Neuromuscular Blocking Agents:** Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly. **Carbamazepine:** The concomitant oral administration of verapamil and carbamazepine may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness. **Cimetidine:** Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination half-life. **Lithium:** Oral verapamil therapy may result in a lowering of serum lithium levels in patients receiving chronic oral lithium therapy. A dose adjustment of the lithium may be necessary. **Rifampin:** Therapy with rifampin may markedly reduce oral verapamil bioavailability. **Phenobarbital:** Phenobarbital therapy may increase verapamil clearance. **Cyclosporine:** Verapamil therapy may increase serum levels of cyclosporine. **Theophylline:** Verapamil may inhibit the clearance and increase the plasma levels of theophylline. **Sulfinpyrazone:** Increased clearance and decreased bioavailability of verapamil may occur. **Inhalation Anaesthetics:** When used concomitantly, inhalation anaesthetics and calcium antagonists such as verapamil, should be titrated carefully because additive hemodynamic depressive effects have been observed.

**ADVERSE REACTIONS:** In 4,826 patients treated with ISOPTIN Tablets for arrhythmias, angina or hypertension, the overall adverse reaction rate in these patients was 37.1% and the dropout rate was 10.2%. The majority of these patients were seriously ill and treated under emergency drug regulations. In controlled pivotal studies with 128 patients treated with ISOPTIN-SR Tablets for hypertension, the overall adverse reaction rate was 21.7% and the dropout rate was 3.9%. The most common adverse reactions were constipation (7.3%), dizziness (3.2%), and nausea (2.7%). In hypertension studies, constipation occurred in 18.5% of patients on ISOPTIN and 4.7% of patients on ISOPTIN-SR. The most serious adverse reactions reported with verapamil are heart failure (1.8%), hypotension (2.5%), A-V Block (1.2%) and rapid ventricular response (See WARNINGS). The following adverse reactions divided by body system have been reported in clinical trials or marketing experience. When incidences are shown, they are calculated based on the 4,954 (4,826 + 128) patient base. **Cardiovascular:** Hypotension (2.5%), edema (2.1%), CHF / pulmonary edema (1.9%), bradycardia (1.4%), total A-V block -1°, 2°, 3°- (1.2%), A-V block 2°, 3° (0.8%). **Central Nervous System:** Dizziness (3.2%), headaches (2.2%), fatigue (1.7%). **Gastro-intestinal:** Constipation (7.3%), nausea (2.7%). **The following reactions were reported in ≤1.0% of patients: Cardiovascular:** Flushing, angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura, syncope, severe tachycardia, developing or worsening of heart failure, development of rhythm disturbances, ventricular dysrhythmias, painful coldness and numbness of extremities. **Central Nervous System:** Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, excitation, depression, rotary nystagmus, vertigo, tremor, extrapyramidal disorders, muscle fatigue, hyperkinesis. **Gastrointestinal:** Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting. **Respiratory:** Dyspnea, bronchospasm. **Urogenital:** Gynecomastia, increased frequency of urination, spotty menstruation, oligomenorrhea, impotence. **Hematologic and Lymphatic:** Ecchymosis or bruising. **Skin:** Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson Syndrome, erythema multiforme, pruritis. **Special Senses:** Blurred vision, diplopia. Hepatotoxicity with elevated enzymes (SGOT, SGPT, alkaline phosphatase) and bilirubin levels, jaundice and associated symptoms of hepatitis with cholestasis have been reported (See WARNINGS). In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or flutter, ventricular rates below 50 at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

**DOSAGE AND ADMINISTRATION: ISOPTIN-SR Tablets:** Mild To Moderate Essential Hypertension (See INDICATIONS). ISOPTIN-SR Tablets should be taken with food. The dosage should be individualized by titration depending on patient tolerance and responsiveness to verapamil. Titration should be based on therapeutic efficacy and safety, evaluated weekly and approximately 24 hours after the previous dose.The usual initial adult dose is 180-240 mg/day. If required, the dose may be increased up to 240 mg twice a day. A maximum daily dose of 480 mg should not be exceeded. Recommended dosing intervals for specific daily dosages are as follows: **a)** 180 mg once each morning with food **OR** 240 mg once each morning with food **b) 360 mg:** 180 mg each morning + 180 mg each evening, with food **OR** 240 mg each morning + 120 mg each evening, with food **c) 480 mg:** 240 mg each morning + 240 mg each evening, with food. The antihypertensive effects of ISOPTIN-SR are evident within the first week of therapy. Optimal doses are usually lower in patients also receiving diuretics since additive antihypertensive effects can be expected. **Elderly:** Lower dosages of ISOPTIN-SR i.e.,120 mg a day, may be warranted in elderly patients (i.e., ≥65 years) (See PRECAUTIONS). The dosage should be carefully and gradually adjusted depending on patient tolerability and response. **Patients With Impaired Liver and Renal Function:** ISOPTIN-SR should be administered cautiously to patients with liver or renal function impairment. The dosage should be carefully and gradually adjusted depending on patient tolerance and response. These patients should be monitored carefully for abnormal prolongation of the PR interval or other signs of overdosage. ISOPTIN-SR should not be used in severe hepatic dysfunction (See WARNINGS). **Switching From ISOPTIN Tablets to ISOPTIN-SR:** When switching from ISOPTIN Tablets to ISOPTIN-SR the total daily dose in milligrams may remain the same. **ISOPTIN-SR 240 mg TABLETS:** Each light-green, scored, capsule shaped, film-coated with 2 triangles embossed on one side contains 240 mg of verapamil hydrochloride. Available in bottles of 100 and 500 tablets. **ISOPTIN-SR 180 mg TABLETS:** Each light-pink, football-shaped, film-coated tablet with KNOLL on one side and SR, scored, 180 on the other, contains 180 mg verapamil hydrochloride. Available in bottles of 100 tablets. **ISOPTIN-SR 120 mg TABLETS:** Each off-white, biconvex, round film-coated tablet with 120 SR embossed on one side, KNOLL on the other side, contains 120 mg verapamil hydrochloride. Available in bottles of 100 tablets. **SPECIAL NOTE TO PHARMACISTS:** The ISOPTIN-SR 240 mg tablet may be split in half. Crushing ISOPTIN-SR tablets is not recommended since the sustained-release effect will be altered by damage to the tablet structure. Use of ISOPTIN-SR 120 mg is recommended. Product monograph available on request.

**REFERENCES:**


**180 mg: 1.** Post Marketing Surveillance Study. Treatment of hypertension in primary care - A clinical evaluation of the safety and efficacy of ISOPTIN® SR (verapamil hydrochloride). *Today's Ther Trends* 1993;10(4):215.24. **240 mg: 1.** McCormack PME et al. The efficacy and duration of action of sustained-release verapamil in essential hypertension. *J Cardiovasc Pharmacol* 1989;13(Suppl 4):S34-7. **2.** Edmonds D et al. Verapamil 240 mg: effective blood pressure reduction with a single daily dose? *J Hypertens* 1986;4(Suppl 5):S455-7. **3.** Novo S et al. Noninvasive blood pressure monitoring evaluation of verapamil slow-release 240 mg antihypertensive effectiveness. *J Cardiovasc Pharmacol* 1989;13(Suppl 4):S38-41. **4.** IMS Canada, "Canadian Disease and Therapeutic Index", MAT/JUNE 1993.



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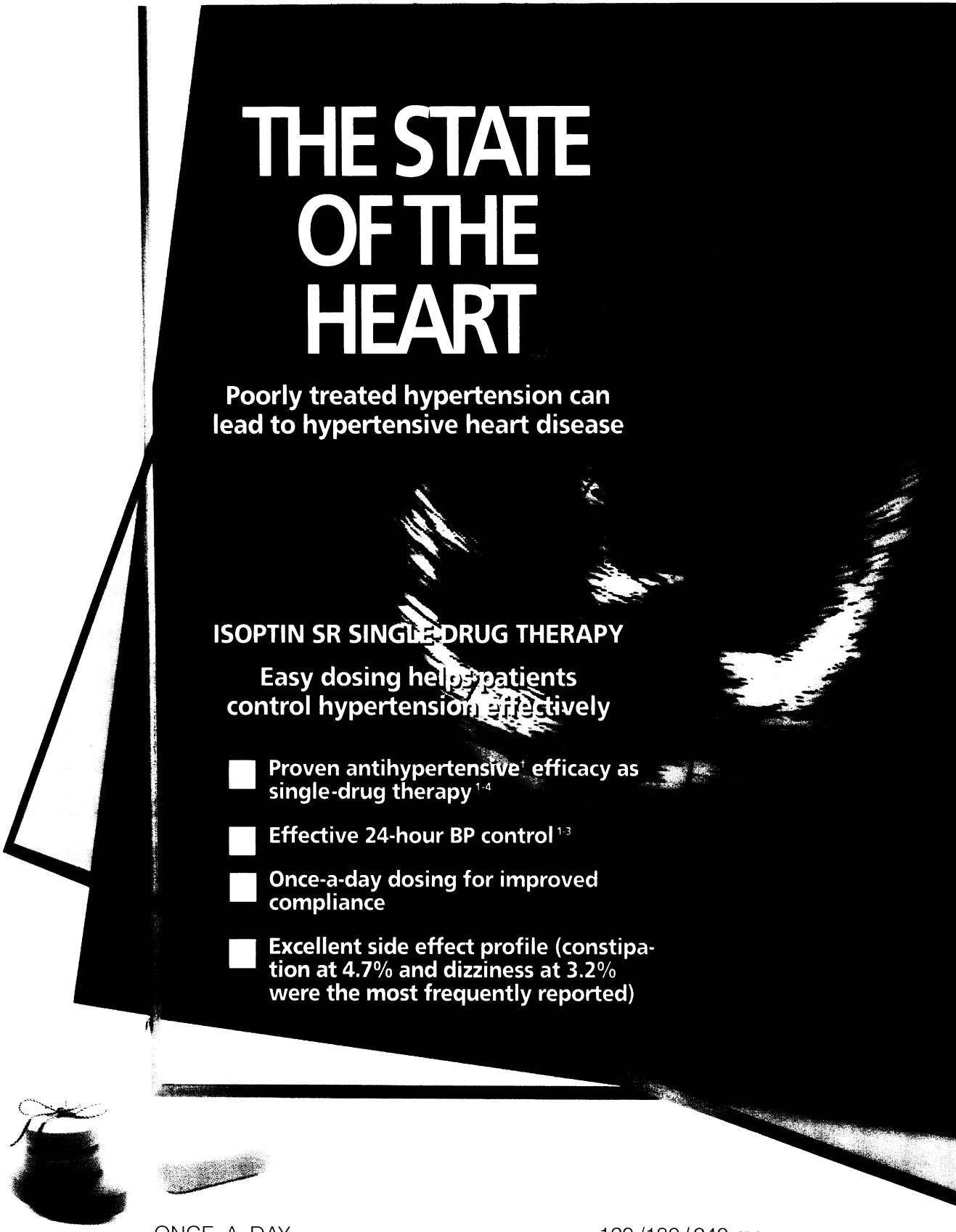
# THE STATE OF THE HEART

**Poorly treated hypertension can lead to hypertensive heart disease**



## ISOPTIN SR SINGLE-DRUG THERAPY

**Easy dosing helps patients control hypertension effectively**

- Proven antihypertensive[†] efficacy as single-drug therapy[1-4]
- Effective 24-hour BP control[1-3]
- Once-a-day dosing for improved compliance
- Excellent side effect profile (constipation at 4.7% and dizziness at 3.2% were the most frequently reported)



ONCE-A-DAY 120/180/240 mg

# ISOPTIN® SR

(verapamil HCl sustained release tablets)

ONE DRUG. ONCE A DAY.

[†]Should normally be used when diuretics or beta-blockers are unacceptable.

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